

## What do we know about micronutrients in critically ill patients – a narrative review, Intensive Care Medicine

### Authors

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## VITAMIN A

**Table S1: Vitamin A in critically ill population: Observational studies**

<b>Study</b>	<b>Study design</b>	<b>Patient population</b>	<b>Results</b>	<b>Conclusion</b>
<p><b>Antioxidant status in patients with acute respiratory distress syndrome (1999)</b></p> <p><b>Metnitz PG, PMID: 10193545</b></p>	Observational study	08 patients with ARDS	<ol style="list-style-type: none"> <li>1. Plasma levels of alpha-tocopherol, ascorbate, beta-carotene and selenium were reduced from the onset of illness.</li> <li>2. Lipid peroxidation products [Malondialdehyde (MDA)] plasma levels were increased throughout the illness.</li> <li>3. ROS generation from neutrophils was normal on D0 and decreased to D6 in ARDS patients</li> </ol>	<ul style="list-style-type: none"> <li>• The antioxidative system is severely compromised in patients with ARDS</li> <li>• Plasma levels of alpha-tocopherol, ascorbate, beta-carotene and selenium are decreased</li> <li>• Elevated MDA levels provide further evidence of massive oxidative stress</li> </ul> <p>The routine replacement of micronutrients according to recommended daily allowances was inadequate to compensate for the increased requirements</p>
<p><b>Plasma antioxidant status in septic critically ill patients: a decrease over time (2008)</b></p> <p><b>Doise JM, PMID: 18353115</b></p>	Observational prospective, cohort study	56 consecutive septic patients	<ol style="list-style-type: none"> <li>1. An equivalent time decline of total plasma antioxidant capacity (TAC level) was observed in the two septic populations whatever the severity</li> <li>2. TAC was statistically linked to uric acid, proteins in particular albumin and bilirubin</li> <li>3. No correlation was found between TAC level and any vitamin (A, C and E)</li> <li>4. A sharp and persistent decrease in vitamin C concentrations was underlined</li> </ol>	<ul style="list-style-type: none"> <li>• TAC, unaffected at first, deteriorated over time whatever the severity of the infection in these critically ill patients</li> <li>• TAC, unable to distinguish severe sepsis and septic shock, is unlikely to be a particularly useful outcome measure</li> </ul>

<p><b>Prevalence of vitamin deficiencies on admission: relationship to hospital mortality in critically ill patients (2009)</b></p> <p><b>Corcoran TB, PMID: 19400489</b></p>	<p>Observational Prospective, cohort study</p>	<p>129 consecutive, critically ill patients who were emergently admitted to intensive care</p>	<ol style="list-style-type: none"> <li>1. 55 patients (43%) had a biochemical deficiency of one of the five vitamins (Vitamins A, E, B1, B12 and folate) on admission to the intensive care unit</li> <li>2. Moderate correlations with C-reactive protein concentrations were demonstrated for Vitamins B12, A and E</li> <li>3. Hospital mortality was significantly associated with age, APACHE II score, admission and maximum Sequential Organ Failure Assessment scores and admission source in the univariate analyses</li> <li>4. Multivariate analysis did not demonstrate an association between biochemical deficiency and mortality</li> </ol>	<ul style="list-style-type: none"> <li>• Biochemical deficiencies of water-soluble and antioxidant vitamins are common on admission in unplanned or emergency admissions to the intensive care unit, an independent association with hospital mortality was not demonstrated</li> </ul>
<p><b>Serum concentrations of vitamin A and oxidative stress in critically ill patients with sepsis (2009)</b></p> <p><b>Nogueira CR, PMID: 19721904</b></p>	<p>Observational prospective, single-center case-control study</p>	<p>46 critically ill patients</p>	<ol style="list-style-type: none"> <li>1. Reduced levels of retinol and beta-carotene were found in 65.2% and 73.9% of the patients, respectively</li> <li>2. Among the patients who presented lower concentrations of CRP it was found higher beta-carotene inadequacy (64.8%) and 50% of retinol inadequacy</li> <li>3. There was no significant difference as regards retinol, TBARS and APACHE II levels among the patients with and without nutritional support</li> </ol> <p>However, higher levels of CRP (p = 0.001)</p>	<ul style="list-style-type: none"> <li>• Septic patients presented an important inadequacy of retinol and beta-carotene</li> <li>• The present study brings elements to the elaboration/review of the nutritional protocol directed to the group studied, especially as regards vitamin A intake</li> </ul>

			and lower levels of serum beta-carotene ( $p = 0.047$ ) were found in patients without nutritional support	
<p><b>Circulating retinol binding protein 4 in critically ill patients before specific treatment: prognostic impact and correlation with organ function, metabolism and inflammation (2010)</b></p> <p><b>Koch A, PMID: 20932285</b></p>	Observational Prospective single-center, study	123 patients at admission to a medical ICU before initiation of specific intensive care treatment measures and compared to 42 healthy controls	<ol style="list-style-type: none"> <li>1. Serum RBP4 was significantly reduced in ICU patients, independently of sepsis</li> <li>2. Patients with liver cirrhosis as the primary underlying diagnosis for ICU admission had significantly lower RBP4 levels</li> <li>3. In all ICU patients, serum RBP4 closely correlated with liver function and increased with renal failure</li> <li>3. Acute phase proteins were inversely correlated with RBP4 in sepsis patients</li> <li>4. Serum RBP4 levels correlated with endogenous insulin secretion (C-peptide) and insulin resistance (HOMA index)</li> <li>5. Low serum RBP4 upon admission was an adverse predictor of short-term survival in the ICU</li> </ol>	<ul style="list-style-type: none"> <li>• Serum RBP4 concentrations are significantly reduced in critically ill patients.</li> <li>• The strong associations with hepatic and renal function, insulin resistance and acute mortality collectively suggest a role of RBP4 in the pathogenesis of critical illness, possibly as a negative acute phase reactant, and allow a proposition as a potential novel biomarker for ICU patients</li> </ul>
<p><b>Vitamin A Plasma Levels in COVID-19 Patients: A Prospective Multicenter Study and Hypothesis (2021)</b></p>	Observational prospective, multicenter cross-sectional study	40 SARS-CoV-2 infected hospitalised patients	<ol style="list-style-type: none"> <li>1. Reduced vitamin A plasma levels correlated significantly with increased levels of inflammatory markers (CRP, ferritin) and with markers of acute SARS-CoV-2 infection (reduced lymphocyte count, LDH)</li> <li>2. Vitamin A levels were significantly lower in hospitalized patients than in</li> </ol>	<ul style="list-style-type: none"> <li>• Vitamin A plasma levels in COVID-19 patients are reduced during acute inflammation and that severely reduced plasma levels of vitamin A are significantly associated with ARDS and mortality</li> </ul>

<p><b>Tepasse PR, PMID: 34202697</b></p>			<p>convalescent persons (<math>p &lt; 0.01</math>)</p> <p>3. Of the hospitalized patients, those who were critically ill showed significantly lower vitamin A levels than those who were moderately ill (<math>p &lt; 0.05</math>)</p> <p>4. Vitamin A plasma levels below 0.2 mg/L were significantly associated with the development of ARDS (<math>p = 0.048</math>) and mortality (<math>p = 0.042</math>)</p>	
<p><b>Significantly Reduced Retinol Binding Protein 4 (RBP4) Levels in Critically Ill COVID-19 Patients (2022)</b></p>	<p>Observational, prospective, multicenter, cross-sectional</p>	<p>283 hospitalized COVID-19 patients (Nasopharyngeal swab PCR positive)</p>	<ol style="list-style-type: none"> <li>1. Reduced RBP4 plasma levels significantly correlated with impaired liver function and elevated inflammatory markers (CRP, lymphocytopenia).</li> <li>2. RBP4 levels were decreased in hospitalized patients with critical illness compared to nonpatients (<math>p &lt; 0.01</math>).</li> <li>3. Significantly lower vitamin A levels were detected in hospitalized patients regardless of disease severity.</li> </ol>	<ul style="list-style-type: none"> <li>• RBP4 plasma levels are significantly reduced in critically ill COVID-19 patients during acute inflammation, and vitamin A levels are significantly reduced in patients with moderate/severe/critical illness during the acute phase of illness</li> </ul>
<p><b>Micronutrient intake from enteral nutrition in critically ill adult patients: A retrospective observational study (2022)</b></p> <p><b>Breik L, PMID: 34999384</b></p>	<p>Observational Single-center retrospective study</p>	<p>57 patients during the first 7 d of ICU admission, mechanically ventilated and prescribed exclusive enteral nutrition (EN)</p>	<ol style="list-style-type: none"> <li>1. EN delivery met the recommended dietary intake for vitamin B12, vitamin C, thiamine, and iron and did not meet the recommended dietary intake for vitamin D, vitamin A, folate, zinc, and selenium</li> <li>2. No micronutrients exceeded the upper level of intake</li> </ol>	<p>EN delivery met the recommended intake for four micronutrients, did not meet the recommended intake for five micronutrients, and did not exceed the upper level of intake for any micronutrient when approximately 50% energy adequacy was achieved types</p>

**Table S2: Vitamin A in critically ill population: Interventional studies**

Study	Study design/Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p><b>Enteral feeding with a solution enriched with antioxidant vitamins A, C, and E enhances the resistance to oxidative stress (2000)</b></p> <p><b>Preiser JC, PMID: 11153621</b></p>	<p>Prospective, randomized, double-blinded, placebo-controlled study</p>	<p>37 critically ill patients</p>	<p>Administration of enteral formula supplemented with vitamins A (67 microg/dL), C (13.3 mg/dL), and E (4.94 mg/dL) Vs isocaloric and isonitrogenous control solution, over 7 days</p>	<p>No significant difference in documented infection and survival (ICU and 28-day)</p>	<p>1. Intervention significantly increased the concentration of plasma beta-carotene and plasma and LDL-bound alpha-tocopherol (p &lt; 0.05)</p> <p>2. Improved LDL resistance to oxidative stress (p &lt; 0.05)</p>
<p><b>Effects of supplementation of antioxidant vitamins and lipid peroxidation in critically ill patients (2013)</b></p> <p><b>Nogueira CR, PMID: 24160231</b></p>	<p>Randomised Controlled Trial</p>	<p>34 critically ill patients</p>	<p>Daily supplementation of enteral 10,000 IU of vitamin A, 400 mg of vitamin E and 600 mg of vitamin C Vs standard diet, over 8 days</p>	<p>No significant differences in mechanical ventilation, hospitalization days, mortality and incidence of infection</p>	<p>Significantly lower serum concentrations of malondialdehyde (MDA) &amp; vitamin E and higher serum levels of vitamin C in intervention group after supplementation</p>
<p><b>Vitamin A treatment for severe sepsis in humans; a prospective randomized double-blind placebo-controlled clinical trial (2019)</b></p>	<p>Prospective randomized double-blind placebo-controlled clinical trial</p>	<p>63 patients with sepsis and septic shock</p>	<p>Vitamin A supplementation (100 000 UI/day) intramuscularly Vs placebo, over 7 days</p>	<p>No significant difference in 28-day mortality</p>	<p>1. The ICU length of stay was slightly, but not significantly reduced by approximately 2 days in the intervention arm</p> <p>2. The average number of days on the ventilator and</p>

<b>Cherukuri L, PMID: 30661700</b>					pressor agents were similar in two groups
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## THIAMINE

**Table S3: Thiamine/vitamin B1 in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<b>Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study (2016)</b>  <b>Donnino MW, PMID: 26771781</b>	Randomized, double-blind, placebo-controlled trial	88 adult patients with septic shock and elevated lactate (> 3 mmol/L)	Thiamine 200 mg or matching placebo twice daily for 7 days or until hospital discharge	1. No difference in shock reversal (> 24 hours off all vasopressors), APACHE II score at 24 hours, SOFA score at 24 hours, ICU and hospital length of stay or in-hospital mortality 2. Statistically significant decrease in mortality over time in the predefined, thiamine – deficient subgroup within the intervention arm (p = 0.047)	1. No difference between intervention and placebo groups in lactate levels 24 hours after the first dose 2. Significantly lower lactate level at 24 hours of first dose observed in the predefined thiamine – deficient subgroup within the intervention arm (p = 0.03)
<b>Thiamine as a Renal Protective Agent in Septic Shock. A Secondary Analysis of a Randomized, Double-Blind, Placebo-controlled Trial (2017)</b>  <b>Moskowitz A, PMID: 28207287</b>	Secondary analysis of Donnino MW, PMID: 26771781	70 patients enrolled in the original trial at the coordinating centre	IV thiamine 200 mg or placebo twice daily for 7 days	More patients in the placebo group than in the thiamine group were started on RRT (p = 0.04)	The worst creatinine levels were higher in the placebo group than in the thiamine group (P = 0.05)
<b>Intravenous thiamine as an adjuvant therapy for hyperlactatemia in septic shock patients (2019)</b>  <b>Harun NF et al, Crit Care Shock (2019) 22:288-298</b>	Prospective Randomised Controlled Trial	72 patients with septic shock and hyperlactatemia (lactate $\geq$ 2 mmol/l).	IV thiamine 200 mg thrice daily for 3 days Vs placebo	No significant difference in 1. Time for shock reversal (duration of vasopressors being weaning off) 2. Changes of the SOFA score over 72 hours 3. ICU length of stay 4. ICU mortality rate	No significant difference in relative lactate changes over 24 hours
<b>Efficacy of Thiamine in the Treatment of Postcardiac</b>	Randomized, double-	37 out-of-hospital cardiac arrest	IV thiamine 100mg every 8 h for 7 days	No significant differences in 1. All-cause 28-day mortality	No significant differences in 1. Serum 100B level at 72 h



<b>Arrest Patients: A Randomized Controlled Study (2020)</b>  <b>Pradita-Ukrit S, PMID: 32587766</b>	blinded, placebo-controlled study	(OHCA) patients	Vs placebo	2. Neurological outcome at hospital discharge 3. ICU length of stay	2. Serum lactate level and clearance at 24, 48, and 72 h
<b>Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients with Septic Shock: The VITAMINS Randomized Clinical Trial (2020)</b>  <b>Fujii T, PMID: 31950979</b>	Multicenter, open-label, randomized clinical trial	216 patients fulfilling the Sepsis-3 definition of septic shock	IV vitamin C (1.5 g every 6 hours), hydrocortisone (50 mg every 6 hours), and thiamine (200 mg every 12 hours) Vs control, given IV hydrocortisone 50mg 6 hourly alone, until shock resolution or up to 10 days	No significant difference in 1. Duration of time alive 2. Being free of vasopressor administration up to day 7	1. No significant differences in 28-day and 90-day ICU mortality; 28-day hospital mortality; 28-day cumulative vasopressor-free days; 28-day cumulative mechanical ventilation-free days; 28-day renal replacement therapy-free days; Change in SOFA score at day 3; 28-day ICU free-days; Hospital length of stay 2. Significant difference in 90-day hospital mortality (95% CI, 0.69-2.00)
<b>Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial (2020)</b>  <b>Iglesias J, PMID: 32194058</b>	Randomized, double-blinded, placebo-controlled trial	137 septic and septic shock patients	IV Vitamin C 1.5g every 6 hours, thiamine 200mg every 12 hours, and hydrocortisone 50mg every 6 hours for a maximum of 4 days Vs matched placebo	No significant differences in 1. ICU and hospital mortality ICU and hospital LOS	Statistically significant difference seen in the time patients required vasopressors ( $p < .001$ )  No statistically significant change in 1. SOFA score 2. Ventilator free days Clearance of procalcitonin
<b>Effects of thiamine on vasopressor requirements in patients with septic shock: a prospective randomized controlled trial (2020)</b>  <b>Petsakul S, PMID: 33167911</b>	Prospective randomized double-blind placebo-controlled trial	50 patients with septic shock who required vasopressors within 1–24 h of admission	200 mg of IV thiamine Vs placebo every 12 hours for 7 days or until hospital discharge	1. Greater lactate clearance in intervention group ( $p = 0.024$ ) 2. No difference in 28-day mortality	1. Significant reduction in vasopressor dependency index at 24 hours ( $p = 0.02$ ) but not at 4 days and at 7 days 2. No difference in vasopressor-free days 3. No difference in changes in SOFA scores from baseline

<p><b>A multicenter randomized clinical trial of pharmacological vitamin B1 administration to critically ill patients who develop hypophosphatemia during enteral nutrition (The THIAMINE 4 HYPOPHOSPHATEMIA trial) (2021)</b></p> <p>Deane AM, PMID: 34388414</p>	<p>Open-label, parallel-group, randomised, controlled trial</p>	<p>90 critically ill adult patients with a serum phosphate <math>\leq 0.65</math> mmol/L within 72 h of commencing enteral nutrition</p>	<p>IV thiamine 200 mg twice daily for a maximum of seven days Vs usual care</p>	<p>No significant differences in</p> <ol style="list-style-type: none"> <li>1. Days of vasopressor administration</li> <li>2. Deaths</li> </ol>	<p>No significant differences in</p> <ol style="list-style-type: none"> <li>1. Blood lactate over the entire 7 days of treatment</li> <li>2. Percentage change from lactate pre-randomization to T = 24 h</li> </ol>
<p><b>Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients with Sepsis: The VICTAS Randomized Clinical Trial (2021)</b></p> <p>Sevransky JE, PMID: 33620405</p>	<p>Multicenter, randomized, double-blind, adaptive-sample-size, placebo-controlled trial (Early trial termination)</p>	<p>501 patients with acute respiratory and/or cardiovascular dysfunction caused by suspected infection with planned ICU admission</p>	<p>IV vitamin C (1.5 g), thiamine (100 mg), and hydrocortisone (50 mg) every 6 hours for 96 hours or until discharge from the intensive care unit or death Vs matching placebo</p>	<p>No difference in</p> <ol style="list-style-type: none"> <li>1. 30-day mortality</li> <li>2. ICU mortality</li> </ol> <p>ICU and hospital lengths of stay</p>	<p>No difference in</p> <ol style="list-style-type: none"> <li>1. Number of consecutive ventilator- and vasopressor-free days in the first 30 days</li> <li>2. ICU delirium- and coma-free days</li> <li>3. Kidney replacement therapy-free days at day 30</li> </ol> <p>Change of SOFA score between pre-randomization and day 4</p>
<p><b>Associations between early thiamine administration and clinical outcomes in critically ill patients with acute kidney injury (2022)</b></p> <p>Li X, PMID: 34392848</p>	<p>Case-control study</p>	<p>Critically ill patients with AKI within 48 h after ICU admission - 734 patients who received thiamine in the early stage were matched to 734 patients</p>	<p>Administration of <math>\geq 100</math> mg of IV thiamine within 48 h after ICU admission Vs no thiamine</p>	<ol style="list-style-type: none"> <li>1. Lower in-hospital mortality (<math>p &lt; 0.001</math>) in thiamine group</li> <li>2. Lower 90-day mortality (<math>p &lt; 0.001</math>) in thiamine group</li> <li>3. Sub-group analysis <ol style="list-style-type: none"> <li>a. Thiamine use associated with lower in-hospital mortality in patients with stages 1 to 2 AKI</li> <li>b. Early thiamine use was associated with improved short-term survival in critically ill patients with AKI</li> </ol> </li> </ol>	<ol style="list-style-type: none"> <li>1. Thiamine use was associated with recovery of renal function (<math>p &lt; 0.001</math>)</li> </ol>

**Table S4: Thiamine in critically ill patients: Currently ongoing trials**

Patient population	Estimated enrollment	Primary Aim	Study Design	Trial Identifier
Patients with septic shock	80 patients	Comparison of mortality rate between intervention (thiamine supplemented 200 mg twice daily for 7 days) and control group	Retrospective	NCT05840718

## **VITAMIN B2 AND B3**

**Table S5: Vitamin B2/B3 in critically ill population: Observational studies**

<b>Study</b>	<b>Study design</b>	<b>Patient population</b>	<b>Results</b>	<b>Conclusions</b>
<b>Subclinical riboflavin deficiency is associated with outcome of seriously ill patients (1989)</b>  <b>Shenkin SD, PMID: 16837300</b>	Observational study	152 patients in the ICU	Patients who died in ICU or within one week of discharge were found to have significantly poorer riboflavin status than those who survived, but the majority of these measurements were within the normal range	<ul style="list-style-type: none"> <li>• Normal ranges established on a healthy population may not be appropriate in investigation of vitamin nutritional status in seriously ill patients</li> <li>• Riboflavin status is a risk factor in critically ill patients, and that subclinical riboflavin depletion may affect outcome</li> </ul>
<b>Persistent hypotension in the ICU: A Case Series of Niacin Deficiency (2020)</b>  <b>Saliccioli JD, Am J Respir Crit Care Med 2020; 201: A5170</b>	Case series	06 patients with undetectable levels of serum niacin over a period of 08 months	3/6 patients – hypotension and septic shock; 4/6 – hypoglycaemia; 2/6 – delirium; 1/6 – seizures; 4/6 – needed vasopressor support; 2/6 – bradycardia; 4/6 – cortisol level performed and normal; 2/6 – dead at 28-day follow up	Highlights the relationship between critical illness, hypotension and hypoglycaemia inpatients with intact adrenal function and niacin deficiency

**Table S6: Vitamin B2/B3 in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p><b>Riboflavin status in acutely ill patients and response to dietary supplements (2009)</b></p> <p><b>Gariballa S, PMID: 19644132</b></p>	<p>Randomised controlled trial</p>	<p>297 hospitalized, acutely ill adult patients</p>	<p>Daily oral nutritional supplement containing 1.3 mg of riboflavin or a placebo for 6 weeks</p>	<p>1. Riboflavin status improves significantly in the supplement group at 6 weeks compared with the placebo group, but status declines between 6 weeks and 6 months, after patients stop taking the supplements                  2. No significant correlation between erythrocyte glutathione reductase activation coefficient (EGRAC) and either total energy or riboflavin intakes</p>	<p>Significant correlations between</p> <p>1. Total energy intake and riboflavin intakes both in hospital and at home (<math>p &lt; .0001</math>)                  2. Smokers and patients with chronic obstructive pulmonary disease (COPD) have lower riboflavin status (high EGRAC values) compared with nonsmokers and those without COPD</p>

## VITAMIN B6

**Table S7: Vitamin B6 in critically ill population: Observational studies**

Study	Study design	Patient population	Results	Conclusions
<p><b>Higher plasma pyridoxal 5'-phosphate (PLP) is associated with better blood glucose responses in critically ill surgical patients with inadequate vitamin B-6 status (2011)</b></p> <p>Hou C-T, PMID: 21349613</p>	observational cross-sectional study	Thirty-four patients in the surgical intensive care unit	<ol style="list-style-type: none"> <li>1. The mean serum glucose concentration of both groups indicated patients was in the hyperglycemic state (serum glucose &gt; 126 mg/dL)</li> <li>2. Mean serum glucose concentration significantly decreased by day 7 in the adequate vitamin B-6 group, whereas patients still remained in the hyperglycemic state (serum glucose &gt; 126 mg/dL) in the deficient vitamin B-6 group</li> <li>3. Significantly correlations of relatively higher plasma PLP at admission (day 1) with the reduction of blood glucose concentration (<math>r(s) = 0.72, p = 0.029</math>) on day 7 in the deficient vitamin B-6 group</li> </ol> <p>Erythrocyte PLP concentration was positively associated with blood glucose level (<math>r(s) = 0.88, p = 0.002</math>) at admission in the deficient vitamin B-6 group after adjusting for age, gender, APACHE II score, diabetic history and insulin therapy</p>	<ul style="list-style-type: none"> <li>• Surgically ill patients with adequate plasma PLP concentration at admission showed improved blood glucose response at day 7</li> </ul> <p>Higher plasma PLP at admission was a major contributing factor in the reduction of glucose concentration in critically ill surgical patients with deficient vitamin B-6 status</p>
<p><b>Higher Plasma Pyridoxal Phosphate Is Associated with Increased Antioxidant Enzyme Activities in Critically Ill Surgical Patients (2013)</b></p> <p>Cheng C-H, PMID: 23819116</p>	Observational cross-sectional study	Thirty-seven patients in surgical intensive care unit	Plasma pyridoxal-5'-phosphate was positively associated with the mean superoxide dismutase activity level on day 1 ( $r = 0.42, P < 0.05$ ), day 7 ( $r = 0.37, P < 0.05$ ), and on changes ( $\Delta$ (day 7 – day 1)) ( $r = 0.56, P < 0.01$ ) after adjusting for age, gender, and plasma C-reactive protein concentration	Higher plasma pyridoxal-5'-phosphate could be an important contributing factor in the elevation of antioxidant enzyme activity in critically ill surgical patients

<p><b>Pyridoxal-5'-phosphate (PLP) deficiency is associated with hyperhomocysteinemia regardless of antioxidant, thiamine, riboflavin, cobalamine, and folate status in critically ill patients (2016)</b></p> <p><b>Molina-López J, PMID: 26071632</b></p>	<p>Prospective, multicentre, comparative, observational and analytic study</p>	<p>One hundred and three critically ill patients</p>	<ol style="list-style-type: none"> <li>1. Thiamine, riboflavin, pyridoxine and folate status proved deficient in a large number of patients, being significantly lower in comparison with control group, and significantly decreased at 7th day of ICU stay</li> <li>2. Higher homocysteine was observed in patients compared with control group (<math>p &lt; 0.05</math>) where 31.5 and 26.8 percent of subjects presented hyperhomocysteinemia at initial and final of study, respectively</li> <li>3. Antioxidant status was lower than control group in two periods analysed, and decreased at 7th day of ICU stay (<math>p &lt; 0.05</math>) being associated with PLP deficiency</li> <li>4. PLP deficiency was also correlated with hyperhomocysteinemia at two times measured (<math>r = -0.73</math>, <math>p &lt; 0.001</math>; <math>r = -0.69</math>, <math>p &lt; 0.001</math>, respectively), showing at day 7 an odds ratio of 6.62 in our multivariate model</li> </ol>	<ul style="list-style-type: none"> <li>• Critically ill patients with SIRS show deficient B vitamin and low antioxidant statuses</li> <li>• Despite association found between PLP deficiency and low antioxidant status in critically ill patients, PLP deficiency was only associated with hyperhomocysteinemia regardless of antioxidant, riboflavin, cobalamine, and folate statuses in critically ill patients with SIRS at seventh day of ICU stay</li> <li>• PLP deficient patients presented about six times more risk of cardiovascular disease than non-deficients</li> </ul>
<p><b>Serum micronutrient levels in critically ill patients receiving continuous renal replacement therapy: A prospective, observational study (2022)</b></p> <p><b>Gundogan K, PMID: 35383966</b></p>	<p>Prospective, observational study</p>	<p>Fifty adult ICU patients with AKI</p>	<ol style="list-style-type: none"> <li>1. The median APACHE II score on ICU admission was high at 24</li> <li>2. The median days on CRRT was 2days</li> <li>3. At baseline (within 10-15 minutes of CRRT initiation), serum vitamin C, selenium and zinc were below normal</li> <li>4. Serum vitamin B6 levels at 72 hours on CRRT were significantly lower than at 24 hours (<math>p = 0.011</math>)</li> <li>5. Serum vitamin C values fell significantly at 24 and 72 hours during CRRT (<math>p = 0.030</math> and <math>p = 0.001</math>), respectively, and remained low 24 and 48 hours after CRRT was stopped (<math>p = 0.021</math>)</li> <li>5. 6. At baseline and during CRRT, 96% of participants had at least two or more micronutrient levels below the normal range</li> </ol>	<ul style="list-style-type: none"> <li>• Serum vitamin C, selenium and zinc concentrations were below the normal range at baseline</li> <li>• CRRT was associated with a significant further decrease in levels of vitamin C, selenium and zinc.</li> </ul>

**Table S8: Vitamin B6 in critically ill patients: Interventional**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p><b>Vitamin B6 supplementation increases immune responses in critically ill patients (2006)</b></p> <p><b>Cheng C-H, PMID: 16670691</b></p>	<p>Single-blind intervention study</p>	<p>Fifty-one patients assigned to one of three groups who stayed over 14 days in the intensive care unit</p>	<p>Control (n=20); a daily injection of 50 mg vitamin B-6 (B6 -50, n=15), or 100 mg vitamin B-6 (B6 -100, n = 16) for 14 days</p>	<p>A large dose of vitamin B6 supplementation (50 or 100 mg/day) could compensate for the lack of responsiveness of plasma PLP to vitamin B6 intake, and further increase immune response of critically ill patients.</p>	<p>Total lymphocyte count, T-helper and T-suppressor cell numbers, the percentage of T-lymphocyte cells and T-suppressors significantly increased in the B6 -100 group at the 14th day. There were no significant changes with respect to immune responses in the control group over 14 days.</p>
<p><b>Renal protective effect and clinical analysis of vitamin b 6 in patients with sepsis (2024)</b></p> <p><b>Yao Wang, PMID: 38691102</b></p>	<p>Multicentre experimental randomised controlled trial</p>	<p>128 patients with sepsis who met the entry criteria</p>	<p>Experimental group (n=64); daily vitamin B6 intravenous injections of 300 mg/dL (100 mg/dL*3), for one week or until the patient died. Control group (n=64) injected with 0.9% sodium chloride solution 6 mL intravenously for the given period. Both groups were given routine treatment of sepsis and corresponding treatment of primary disease</p>	<p>No statistical difference between the two groups in the rate of renal replacement therapy and 28 d mortality (<math>p &gt; 0.05</math>). The intensive care unit length of stay and the total hospitalization expenses in the experimental group were significantly lower than those in the control group (<math>p &lt; 0.05</math>)</p>	<p>IL-6, IL-8, TNF-<math>\alpha</math>, and ET-1 levels in the experimental group were significantly lower than those in the control group, the oxidative stress response indicators were significantly improved in the experimental group and the blood urea nitrogen, serum creatinine, and renal resistance index values in the experimental group were significantly lower than those in the control group (<math>p &lt; 0.05</math>)</p>



**FOLATE**

**Table S9 Vitamin B9 (Folate) in critically ill patients: observational studies**

Study	Study design	Patient population	Results	Conclusions
<p><b>Inflammation, vitamin deficiencies and organ failure in critically ill patients (2009)</b></p> <p>Corcoran TB, PMID: 19775037</p>	<p>Nested cohort study</p>	<p>Seventy patients admitted as emergencies to the intensive care unit, who had a stay of greater than 48 hours</p>	<ol style="list-style-type: none"> <li>1. Ten patients died (14.3%) during their hospital stay and mortality was associated with age, admission source and severity of illness scores</li> <li>2. Vitamin B12 concentration was weakly associated with C-reactive protein concentrations on admission to the intensive care unit (r on days one and two = 0.4 [P = 0.002], 0.36 [P = 0.04], respectively) and with the Sequential Organ Failure Assessment score between days two and four (Spearman's r = 0.361 [P = 0.04], 0.42 [P = 0.02] and 0.48 [P = 0.02], respectively)</li> <li>3. Vitamin A concentration was weakly associated with the C-reactive protein concentrations on days one and five (Spearman's r = -0.5 [P = 0.001], -0.4 [P = 0.03], respectively)</li> </ol>	<ul style="list-style-type: none"> <li>• Change in deficiency status of any of the vitamins over time in the first week of intensive care admission did not appear to influence mortality</li> <li>• It was concluded that while weak correlations were identified between vitamins A and B12 and C-reactive protein and Sequential Organ Failure Assessment scores, the importance of these associations and their relationship to hospital mortality remain to be determined</li> </ul>
<p><b>Pyridoxal-5'-phosphate (PLP) deficiency is associated with hyperhomocysteinemia regardless of antioxidant, thiamine, riboflavin, cobalamine, and folate status in critically ill patients (2016)</b></p> <p>Molina-López J, PMID: 26071632</p>	<p>Prospective, multicentre, comparative, observational and analytic study</p>	<p>One hundred and three critically ill patients</p>	<ol style="list-style-type: none"> <li>6. Thiamine, riboflavin, pyridoxine and folate status proved deficient in a large number of patients, being significantly lower in comparison with control group, and significantly decreased at 7th day of ICU stay</li> <li>7. Higher homocysteine was observed in patients compared with control group (p &lt; 0.05) where 31.5 and 26.8 percent of subjects presented hyperhomocysteinemia at initial and final of study, respectively</li> <li>8. Antioxidant status was lower than control group in two periods analysed, and decreased at 7th day of ICU stay (p &lt; 0.05) being associated with PLP deficiency</li> </ol> <p>PLP deficiency was also correlated with hyperhomocysteinemia at two times measured (r = 0.73, p &lt; 0.001; r = -0.69, p &lt; 0.001, respectively), showing at day 7 an odds ratio of 6.62 in our multivariate model</p>	<ul style="list-style-type: none"> <li>• Critically ill patients with SIRS show deficient B vitamin and low antioxidant statuses</li> <li>• Despite association found between PLP deficiency and low antioxidant status in critically ill patients, PLP deficiency was only associated with hyperhomocysteinemia regardless of antioxidant, riboflavin, cobalamine, and folate statuses in critically ill patients with SIRS at seventh day of ICU stay</li> </ul> <p>PLP deficient patients presented about six times more risk of cardiovascular disease than non-deficients</p>

<p><b>Micronutrient Alterations During Continuous Renal Replacement Therapy (CRRT) in Critically Ill Adults: A Retrospective Study (2017)</b></p> <p>Kamel AY, PMID: 28727945</p>	<p>Retrospective chart review</p>	<p>Seventy-five patients who were referred to nutrition support services and had at least 1 serum micronutrient level measured during CRRT (thiamin, pyridoxine, ascorbic acid, folate, zinc, and copper)</p>	<ol style="list-style-type: none"> <li>1. Nine of 56 patients (16%) had below-normal whole blood thiamin concentrations, and 38 of 57 patients (67%) had below-normal serum pyridoxine levels</li> <li>2. Serum ascorbic acid and folate deficiencies were identified among 87% (13 of 15) and 33% (3 of 9) of the study patients, respectively</li> <li>3. Nine of 24 patients had zinc deficiency (38%), and 41 of 68 patients had copper deficiency (60%)</li> <li>4. Of the 75 total subjects, 60 patients (80%) had below-normal levels of at least 1 of the micronutrients measured</li> </ol>	<ul style="list-style-type: none"> <li>• The incidence of various micronutrient deficiencies in critically ill patients who required CRRT was higher than previously reported</li> <li>• Prospective studies are needed to determine the impact of CRRT on micronutrient status and the potential clinical and metabolic efficacy of supplementation in the intensive care unit setting.</li> </ul>
<p><b>Micronutrients in critically ill patients with severe acute kidney injury - a prospective study (2020)</b></p> <p>Ostermann M, PMID: 32001725</p>	<p>Observational study</p>	<p>Fifty-five critically ill patients with severe AKI</p>	<ol style="list-style-type: none"> <li>1. CRRT patients had lower plasma concentrations of citrulline, glutamic acid and carnitine at 24 hrs after enrolment and significantly lower plasma glutamic acid concentrations (74.4 versus 98.2 <math>\mu\text{mol/L}</math>) at day 6 compared to non-CRRT patients</li> <li>2. All amino acids, trace elements, vitamin C and folate were detectable in effluent fluid</li> <li>3. In &gt;30% of CRRT and non-CRRT patients, the plasma nutrient concentrations of zinc, iron, selenium, vitamin D3, vitamin C, tryptophan, taurine, histidine and hydroxyproline were below the reference range throughout the 6-day period</li> </ol>	<ul style="list-style-type: none"> <li>• Altered micronutrient status is common in patients with severe AKI regardless of treatment with CRRT</li> </ul>
<p><b>Folic acid and vitamin B12 as biomarkers of morbidity and mortality in patients with septic shock (2022)</b></p> <p>Gamarra-Morales Y,</p>	<p>Prospective analytical study</p>	<p>Thirty critically ill patients with septic shock</p>	<ol style="list-style-type: none"> <li>1. Mean serum folate was within the reference range stipulated by the laboratory on the first day</li> <li>2. Nevertheless, a total of 21.4 % of the patients had high folate levels, with 14.2 % being folate deficient</li> <li>3. An association was observed between folate (<math>p &lt; 0.012</math>) status and 28-day mortality, and</li> </ol>	<ul style="list-style-type: none"> <li>• This study proposes folate as a novel morbidity-mortality biomarker in critical septic patients, and reinforces the usefulness of B12 as a morbidity biomarker</li> <li>• It is thus suggested that the measurement of folate upon admission and over the first 72 hours of hospital</li> </ul>

PMID: 35156379			<p>the number of days of mechanical ventilation, fraction of inspired oxygen (FiO2) and fibrinogen increased in patients with higher folate levels (<math>p &lt; 0.05</math>)</p> <p>4. In addition, 85.7 % of cases had B12 levels above the reference values, with a correlation being observed between B12 and folate</p>	stay could provide prognostic information about the clinical course and outcome of septic shock patients
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**Table S10: Vitamin B9 (Folate) in critically ill patients: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p><b>Prophylaxis of folate deficiency in acutely ill patients: results of a randomized clinical trial (1988)</b></p> <p>Campillo B, PMID: 3141491</p>	Randomised clinical trial	Hundred and five acutely ill patients immediately following admission to an ICU with evaluation of folate status	<p>patients were fed either orally or by enteral or parenteral nutrition. Three groups were established regardless of the type of nutrition: - Group 1 received 5 mg/day parenteral folinic acid; - Group 2 received 50 mg/week parenteral folinic acid; - Group 3 received no parenteral folinic acid. Before treatment, 19% of the patients presented very low serum folate levels (less than 2.7 ng/ml)</p>	<ol style="list-style-type: none"> <li>1. Among these 83 patients, two who presented very low serum folate developed a rapid and steep drop of blood cell counts within a few days.</li> <li>2. Folate status was not correlated with age, and was inversely correlated with Simplified acute physiology score (SAPS) (<math>p &lt; 0.05</math>)</li> </ol>	<ol style="list-style-type: none"> <li>1. On day 7, out of the 83 patients remaining in the analysis, folate levels showed a significant increase in groups 1 (<math>p &lt; 0.001</math>) and 2 (<math>p &lt; 0.01</math>) and were unchanged in group 3</li> <li>2. There was a significant difference between the three groups (<math>p &lt; 0.001</math>) as well between groups 1 and 2 (<math>p &lt; 10^{-4}</math>)</li> <li>3. The increase in serum folate was significantly greater in group 1 than in group 2 (<math>p &lt; 10^{-4}</math>), and the percentage of patients with low serum folate in group 3 was significantly higher than in group 1 and 2 (<math>p &lt; 0.01</math>)</li> </ol>

## VITAMIN C

**Table S11 Vitamin C in critically ill patients: interventional studies**

Study Title	Level of evidence	Patient population	Intervention	Primary endpoints	Surrogate endpoints
<b>Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery (2009)</b>  <a href="#">Ferrón-Celma I</a> , PMID: 18952228	Randomized placebo-controlled trial	20 septic abdominal surgery patients	Intervention group, patients (n=10) received Vitamin C (450 mg/d of the vitamin in 3 doses) for a 6-day period from 12 h post-surgery,	Postoperative Vitamin C in septic abdominal surgery patients showed an antiapoptotic effect on peripheral blood neutrophils (non-significant reduction in Fas (CD95) expression on CD15-positive peripheral blood neutrophils); while significant reducing caspase-3 and PARP levels, and increasing Bcl-2 levels.	Anti-apoptotic effects are not maintained at all-time points.
<b>Administration of Vitamin C and Vitamin E in Severe Head Injury: A Randomized Double-blind Controlled Trial (2011)</b>  Razmkon A, PMID: 21916138	Randomized placebo-controlled trial	100 patients with brain injury	In intervention group patients received either low-dose Vitamin C (500 mg/d IV) for 7 days; or high-dose Vitamin C (10 g IV on the first day and repeated on the fourth day, followed by vitamin C 4 g/d IV for the remaining 3 days)	No significant reductions in mortality, length of hospitalization or neurological recover. However, high-dose Vitamin C stabilized or reduced the diameter of perilesional hypodense region in subsequent days in 68% of patients ( $P=.01$ ).	No other significant changed occurred in follow-up brain imaging, such as size of hematoma ( $p=0.1$ ), appearance of basal cisterns ( $p=0.82$ ), and midline shift ( $p=0.36$ ).
<b>Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis (2014)</b>  Fowler AA, PMID: 24484547	Randomized placebo-controlled trial	24 patients with severe sepsis	Intervention group patients received either low-dose (50 mg/kg/24 h, n = 8) or high-dose (200 mg/kg/24 h, n = 8) intravenous Vitamin C infusions every six hours for four days.	No adverse safety events were observed in Vitamin C group patients.	Vitamin C group patients had prompt reductions in SOFA scores, also significantly reduction in the proinflammatory biomarkers C-reactive protein and procalcitonin.
<b>Effect of high-dose Ascorbic</b>	Randomized	28 surgical	Intervention group	Mean dose and duration of	28-day mortality was significantly

<p><b>acid on vasopressor's requirement in septic shock (2016)</b></p> <p>Zabet MH, PMID: <a href="#">27162802</a></p>	<p>placebo-controlled trial</p>	<p>critically ill patients with septic shock.</p>	<p>patients received 25 mg/kg intravenous ascorbic acid every 6 h for 72 h.</p>	<p>norepinephrine were significantly lower in the ascorbic (<math>7.44 \pm 3.65</math> vs. <math>13.79 \pm 6.48</math> mcg/min, <math>p=0.004</math> and <math>49.64 \pm 25.67</math> vs. <math>71.57 \pm 1.60</math> h, <math>p=0.007</math>, respectively)</p>	<p>lower in the Vitamin C group (14.28% vs. 64.28%, <math>p=0.009</math>).</p>
<p><b>Vitamin C Pharmacokinetics in Critically Ill Patients: A Randomized Trial of Four IV Regimens (2018)</b></p> <p>de Grooth HJ, PMID: 29522710</p>	<p>Randomized pharmacokinetics trial</p>	<p>20 patients with multiple organ dysfunction</p>	<p>Patients received Vitamin C in a dose of either 2 or 10 g/d as a twice daily bolus infusion or continuous infusion for 48 h</p>	<p>2 g/d dose of Vitamin C was associated with normal plasma concentrations, (with bolus, plasma vitamin C concentrations at 1 h were 29 to 50 mg/L and trough concentrations were 5.6 to 16 mg/; while with continuous, steady-state concentrations were 7 to 37 mg/L at 48 h)</p> <p>10 g/d dose of Vitamin C was associated with supranormal plasma concentrations (with bolus, 1-h concentrations were 186 to 244 mg/L and trough concentrations were 14 to 55 mg/L.; while with continuous, steady-state concentrations were 40 to 295 mg/L at 48 h)</p>	<p>Oxalate excretion and base excess were increased in the 10 g/d dose. Forty-eight hours after discontinuation, plasma concentrations declined to hypovitaminosis levels in 15% of patients.</p>
<p><b>Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial (2019)</b></p> <p>Fowler AA, PMID: 31573637</p>	<p>Multicentre randomized placebo-controlled trial</p>	<p>167 patients with sepsis and ARDS present for less than 24 hours.</p>	<p>In intervention group, intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water every 6 hours for 96 hours.</p>	<p>Vitamin C supplementation did not significantly improve organ dysfunction scores [SOFA score changed from baseline to 96 hours (from 9.8 to 6.8 in the vitamin C group [3 points] and from 10.3 to 6.8 in the placebo group [3.5 points]; difference, -0.10; 95% CI, -1.23 to 1.03; <math>p=0.86</math>).</p>	<p>Also, there were no differences in C-reactive protein levels (54.1 vs 46.1 <math>\mu\text{g/mL}</math>; difference, 7.94 <math>\mu\text{g/mL}</math>; 95% CI, -8.2 to 24.11; <math>p=0.33</math>) and thrombomodulin levels (14.5 vs 13.8 <math>\text{ng/mL}</math>; difference, 0.69 <math>\text{ng/mL}</math>; 95% CI, -2.8 to 4.2; <math>p=0.70</math>) at 168 hours.</p>
<p><b>Safety and effectiveness of</b></p>	<p>Open-label,</p>	<p>60 patients with severe COVID-19</p>	<p>Intervention group</p>	<p>There was no significant difference in</p>	

<p><b>high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial (2021)</b>  <a href="#">JamaliMoghadamSiahkali</a> S, PMID: 33573699</p>	<p>randomized controlled trial</p>	<p>infection.</p>	<p>received 1.5 g vitamin C IV every 6 h for 5 days</p>	<p>the length of ICU stay or mortality.</p>	
<p><b>The Effect of Vitamin C on Pathological Parameters and Survival Duration of Critically Ill Coronavirus Disease 2019 Patients: A Randomized Clinical Trial (2021)</b>  Majidi N, PMID: 34975830</p>	<p>Randomized clinical trial</p>	<p>120 hospitalized critically ill patients infected with COVID-19</p>	<p>31 received one capsule of 500 mg of vitamin C daily for 14 days and 69 in control group received the same nutrition except for vitamin C supplements</p>	<p>After 2 weeks of completion of the intervention (i.e. 4 weeks after randomization) a significantly higher number of patients survived in the intervention group (16.1% vs 2.9% survival, <math>p=0.028</math>).</p>	<p>The vitamin C supplementation had no effect on blood glucose, mean arterial pressure, arterial blood gas parameters, Glasgow Coma Scale, kidney function, cell blood count, haemoglobin, platelet, partial thromboplastin time, albumin and serum electrolytes including sodium, calcium and phosphate.</p>
<p><b>Impact of ascorbic acid in reducing the incidence of vancomycin associated nephrotoxicity in critically ill patients: A preliminary randomized controlled trial (2021)</b>  <a href="#">Hesham El-Sherazy</a> N, PMID: 34621519</p>	<p>Randomized control trial</p>	<p>41 critically ill patients who required intravenous vancomycin for either confirmed or suspected MRSA.</p>	<p>Intervention group (N=21) received Vitamin C orally at a dose of two grams twice daily half an hour before the vancomycin dose</p>	<p>The number of patients suffering vancomycin-associated nephrotoxicity didn't change in either group. However, the mean absolute increase in S.cr concentration was significantly greater in the control group compared to the intervention group (difference of 0.29 mg/dL, 95% CI: 0.02 to 0.54, <math>P</math>-value = 0.036)</p>	<p>No significant difference in the mortality.</p>
<p><b>Effect of Vitamin C on mortality of critically ill patients with severe pneumonia in intensive care unit: a preliminary study (2021)</b>  <a href="#">Mahmoodpoor</a> A, PMID: 34187382</p>	<p>Randomized placebo-controlled trial</p>	<p>80 critically ill patients with severe pneumonia (CURB-65 score &gt;3, one major criterion, or <math>\geq 3</math> minor criteria)</p>	<p>In intervention group, Vitamin C (60 mg/kg/day) was given as a continuous infusion for 96 hours.</p>	<p>Duration of mechanical ventilation and vasopressor use were significantly lower in the intervention group (<math>p</math>: &lt; 0.001 and 0.003, respectively).</p>	<p>No difference in the mortality rate, at 28-days.</p>
<p><b>Role of ascorbic acid infusion in critically ill</b></p>	<p>Randomized placebo-</p>	<p>80 adult (18-64 years) critically</p>	<p>Intervention group (n = 40) received 2.5 g</p>	<p>Patients in Vitamin C group had significantly reduced oxidative stress,</p>	<p>Vitamin C group had shown significant improvement in oxygenation at 96</p>

<p><b>patients with transfusion-related acute lung injury (2022)</b></p> <p>Kassem AB, PMID: 34866234</p>	controlled trial	ill patients diagnosed with TRALI within 6 hours of transfusion	intravenous (IV) ascorbic acid every 6 hours for 96 hours from diagnosis (10 g/d for 4 days)	reduced pro-inflammatory markers and elevated anti-inflammatory marker at 96 hours	hours. Also, had a significantly lower 7-day mortality rate (15%) than the control group (42.5%)
<p><b>Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial (2022)</b></p> <p>Rosengrave P, PMID: 35073968</p>	Randomized placebo-controlled trial	40 patients with septic shock	Patients in intervention group received Vitamin C at a dose of 25 mg/kg of body weight every 6 hours for up to 96 hours, or until death or discharge	Intravenous vitamin C did not provide significant decreases in the mean duration of vasopressor infusion (Vitamin C group 48 (95% CI 35-62) hours versus placebo group 54 (95% CI 41-62) hours (p = 0.52).	There were no differences in the median ICU length of stay or mortality.
<p><b>Effect of Supplementation of Vitamin C and Thiamine on the Outcome in Sepsis: South East Asian Region (2022)</b></p> <p>Ap GR, PMID: 35438278</p>	Randomized controlled trial	80 patients of sepsis	Patients in Vitamin C group received 2g 8 hourly intravenously for five days	No mortality benefit was observed in the groups supplemented with Vitamin C.	
<p><b>Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit (2022)</b></p> <p>Lamontagne F, PMID: 35704292</p>	Multicentre randomized placebo-controlled trial	872 adults ICU patients with proven or suspected infection as the main diagnosis and receiving a vasopressor were randomized within 24 hours of meeting inclusion criteria	435 received vitamin C (at a dose of 50 mg per kilogram of body weight) and 437 received placebo every 6 hours for up to 96 hours	Patients group allocated to vitamin C had higher events (composite of death or persistent organ dysfunction on day 28), 191 of 429 patients (44.5%) in the vitamin C group and in 167 of 434 patients (38.5%) in the control group (risk ratio, 1.21; 95% confidence interval [CI], 1.04 to 1.40; P=0.01).	Other clinically relevant findings (organ-dysfunction scores, biomarkers, 6-month survival, health-related quality of life, stage 3 acute kidney injury, and hypoglycemic episodes) were similar in the both groups.
<p><b>Evaluating Vitamin C in</b></p>	Multicenter,	124 adult patients	In intervention group,	Vitamin C group had shown	Vitamin C group patient had higher



<b>Septic Shock: A Randomized Controlled Trial of Vitamin C Monotherapy (2022)</b>  Wacker DA, PMID: 34982738	randomized placebo-controlled trial	within 24 hours of vasopressor initiation for septic shock	patients received Vitamin C 1.0 g bolus over 30 minutes followed by continuous infusion of 250 mg/hr for 96 hours	decrease in all-cause 28-day mortality arm but did not reach statistical significance. (Vitamin C, 26.7%; placebo, 40.6%; p = 0.10).	incidence of initiation of renal replacement therapy (Vitamin C, 16.7%; placebo, 3.3%; p = 0.015),
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*Footnote:*

*Studies testing vitamin C with 2 or more other interventions, were not included in this table as previous meta-analysis about the combined use of vitamin C with 2 other interventions could not demonstrated significant effects. We further did not show potential effects on long-term outcomes to remain consistent with the given data presentation for the other micronutrients.*

**Table S12 Vitamin C in critically ill patients: ongoing trials**

Patient Population	Estimated Enrollment	Primary Aim	Dose and Duration of Vitamin C	Study Design	Trial Identifier
Adult patients undergoing cardiac surgery	200	Change in lactate during and after cardiopulmonary bypass	2g vitamin C iv before surgery, 2g iv before removing the aortic clamp, 1g iv 8 h after aortic clamp removal and every 8 h thereafter (2 times)	Masking: Triple Centre: Single	ClinicalTrials.gov Identifier: NCT04046861
Severe and critical III COVID-19 adult patients	608	28-day mortality or persistent organ dysfunction at day 28	12g vitamin C every 12 hours for 4 days	Masking: Single Centre: Multicentre	ClinicalTrials.gov Identifier: NCT05694975

Adult medical patients with sepsis and hypotension	60	Change in vitamin C plasma concentration after giving 2 different doses of vitamin C	1.5g or 3g iv vitamin C every 6 hours for 16 doses	Masking: None Centre: Single	ClinicalTrials.gov Identifier: NCT04999137
Adult patients with septic shock	180	Reduction in the dose of vasopressor over 72 hours	6g iv vitamin C in continuous infusion for 24 hours, 3 doses	Masking: Quadruple Centre: Single	ClinicalTrials.gov Identifier: NCT03835286
Adult patients having deep (2nd and/or 3rd degree) burns requiring skin grafting with minimum burn size of $\geq 20\%$ total body surface area	666	28-days composite outcome of persistent organ dysfunction and all-cause mortality	200mg/kg/day iv vitamin C for 96 hours	Masking: Quadruple Centre: Multicentre	ClinicalTrials.gov Identifier: NCT04138394
Adult patients having out-of-hospital cardiac arrest with return of spontaneous circulation and ventricular fibrillation or ventricular tachycardia as first registered cardiac rhythm and Glasgow coma scale (GCS) score $\leq 8$	270	Change in Sequential Organ Failure Assessment (SOFA) score from admission to at 96 hours	1.5g or 5g iv vitamin C 12 hourly for 4 days	Masking: Quadruple Centre: Multicentre	ClinicalTrials.gov Identifier: NCT03509662
During liver transplantation	70	Preventing the postreperfusion syndrome in liver transplantation	1.5g of iv vitamin C during the anhepatic phase of liver transplantation	Masking: Quadruple Centre: Single	ClinicalTrials.gov Identifier: NCT05754242
Adult patients with sepsis and procalcitonin $\geq 2$ ng/ml	152	28-day all-cause mortality	12g iv vitamin C every 12 hourly for 4 days or until ICU discharge	Masking: Double Centre: Multicentre	ClinicalTrials.gov Identifier: NCT05194189
Adult patients with septic shock and acute respiratory distress syndrome	800	Number of deceased participants or with persistent organ	50 mg/kg iv vitamin C every 6 hours for 96 hours (i.e. 200 mg/kg/day and 16 doses in total)	Masking: Quadruple Centre:	ClinicalTrials.gov Identifier: NCT04404387

		dysfunction at 28 days		Multicentre	
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## VITAMIN D

**Table S13: Vitamin D in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p><b>Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study (2011)</b></p> <p>Amrein K, PMID: 21443793</p>	Randomized double-blind placebo-controlled pilot study	25 critically ill patients with vitamin D $\leq$ 20 ng/mL	Single dose of enteral vitamin D3 540,000IU	No significant difference in <ol style="list-style-type: none"> <li>1. Duration of mechanical ventilation</li> <li>2. Hospital length of stay</li> <li>3. ICU length of stay</li> <li>4. Hospital mortality</li> </ol>	No significant difference in <ol style="list-style-type: none"> <li>1. Duration of vasopressor therapy</li> </ol>
<p><b>Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial (2014)</b></p> <p>Amrein K, PMID: 25268295</p>	Randomized double-blind placebo-controlled single-center trial	492 critically ill patients with vitamin D $\leq$ 20 ng/mL	Single dose of enteral vitamin D3 540,000IU followed by monthly 90,000IU for 5 months	Statistically significant <ol style="list-style-type: none"> <li>1. Decrease in hospital length of stay in patients with vitamin D <math>\leq</math> 12 ng/mL (<math>p = 0.04</math>)</li> </ol> No significant difference in <ol style="list-style-type: none"> <li>1. Hospital length of stay</li> <li>2. Mortality; hospital, 6-month</li> </ol>	
<p><b>Randomized controlled trial of calcitriol in severe sepsis (2014)</b></p> <p>Leaf D, PMID: 25029202</p>	Double-blind randomized placebo-controlled study	67 critically ill patients with sepsis	Single dose of calcitriol 2mcg iv	No significant difference in <ol style="list-style-type: none"> <li>1. Mortality; ICU, hospital, 28-days</li> <li>2. ICU length of stay</li> <li>3. Hospital length of stay</li> <li>4. SOFA scores</li> <li>5. Ventilator-free days</li> <li>6. RRT requirement</li> </ol>	Statistically significant <ol style="list-style-type: none"> <li>1. Increase in 1,25D levels (<math>p &lt; 0.001</math>)</li> <li>2. Increase in hCAP-18 mRNA expression</li> </ol> No significant difference in <ol style="list-style-type: none"> <li>1. Cytokine levels (IL-6, TNF-<math>\alpha</math>, IL-10, IL-1<math>\beta</math>, IL-2)</li> <li>2. KIM-1 and NGAL-levels</li> <li>3. Hypercalcemia</li> </ol>
<p><b>A Randomized Study of a Single Dose of Intramuscular Cholecalciferol in Critically Ill Adults (2015)</b></p>	Prospective open label randomized trial	50 critically ill patients with SIRS	Group 1: Single dose of 150,000IU vitamin D3 i.m.	No significant difference in <ol style="list-style-type: none"> <li>1. Mortality</li> <li>2. Hospital length of stay</li> <li>3. ICU length of stay</li> </ol>	Statistically significant <ol style="list-style-type: none"> <li>1. Increase in 25OHD levels from baseline (<math>p = 0.002</math>)</li> </ol>

Nair P, PMID: 26186566			Group 2: Single dose of 300,000IU vitamin D3 i.m.		No significant difference in 1. 1,25(OH)2D levels 2. Inflammation markers (CRP, IL-6)
<b>Effect of Cholecalciferol Supplementation on Vitamin D Status and Cathelicidin Levels in Sepsis: A Randomized, Placebo-Controlled Trial (2015)</b>  Quraishi S, PMID: 26086941	Randomized placebo-controlled trial	30 critically ill patients with sepsis	Group 1: enteral 200,000IU of vitamin D3  Group 2: enteral 400,000IU of vitamin D3  Group 3: placebo	Statistically significant 1. Decrease in hospital length of stay ( $p = 0.03$ ) 2. Decrease in 3-day readmission ( $p < 0.001$ )  No significant difference in 1. ICU length of stay 2. Mortality 30-days	Statistically significant 1. Increase in LL-37 ( $p = 0.02$ ) 2. Increase in 25OHD ( $p = 0.04$ )  No significant difference in 1. CRP
<b>Effect of vitamin D on stress-induced hyperglycaemia and insulin resistance in critically ill patients (2016)</b>  Alizadeh N, PMID: 27091752	Randomized double-blind placebo-controlled trial	59 surgical ICU patients with stress-induced hyperglycemia	Single dose of 600,000IU vitamin D3 i.m.		Statistically significant difference in 1. Serum 25OHD (increase, $p = 0.04$ ) 2. Serum adiponectin (decrease, $p = 0.007$ )  No significant difference in 1. Plasma glucose 2. Plasma insulin 3. Insulin resistance
<b>Effect of vitamin D (3) on the severity and prognosis of patients with sepsis: a prospective randomized double-blind placebo study (2017)</b>  Ding F, PMID: 28625255	Randomized double-blind placebo-controlled trial	57 ICU patients with sepsis with 25OHD3 <30 mcg/L	Single dose of 300,000IU vitamin D3	No significant difference in 1. Mortality 28-days 2. Duration of mechanical ventilation 3. ICU length of stay	

<p><b>Oxidative stress in critically ill ventilated adults: effects of vitamin D(3) and associations with alveolar macrophage function (2018)</b></p> <p>Han J, PMID: 29288250</p>	<p>Pilot double-blind randomized controlled trial</p>	<p>30 mechanically ventilated ICU patients</p>	<p>Group 1: enteral 50,000IU vitamin D3 daily for 5 days</p> <p>Group 2: enteral 100,000IU of vitamin D3 daily for 5 days</p> <p>Group 3: placebo</p>		<p>Significant difference in:</p> <ol style="list-style-type: none"> <li>1. Plasma GSSG (decreased, <math>p &lt; 0.01</math>)</li> </ol> <p>No significant difference in:</p> <ol style="list-style-type: none"> <li>1. Plasma GSH or Cys/CySS redox system</li> </ol>
<p><b>Early High-Dose Vitamin D (3) for Critically Ill, Vitamin D-Deficient Patients (2019)</b></p> <p>Ginde AA, PMID: 31826336</p>	<p>Randomized, double-blind, placebo-controlled, phase 3 trial</p>	<p>1078 ICU patients with vit D &lt; 20 ng/mL</p>	<p>Single enteral dose of 540,000IU vitamin D3</p>	<p>No significant difference in</p> <ol style="list-style-type: none"> <li>1. Mortality 28-days, 90-days</li> <li>2. Hospital length of stay</li> <li>3. Ventilator free days</li> <li>4. AKI and RRT</li> </ol>	<p>No significant difference in</p> <ol style="list-style-type: none"> <li>1. EQ-5D-5L to day 90</li> <li>2. vasopressor use to day 7</li> <li>3. Hypercalcemia, kidney stones, fall-related fractures</li> </ol>
<p><b>Effect of Intravenous 25OHD Supplementation on Bone Turnover and Inflammation in Prolonged Critically Ill Patients (2020)</b></p> <p>Ingels C, PMID: 32215888</p>	<p>Randomized double-blind, placebo-controlled study</p>	<p>24 critically ill patients with prolonged ICU stay (&gt;10 days)</p>	<p>200 mcg i.v. vitamin D3 bolus and 15mcg daily for 10 days</p>	<p>No significant difference in</p> <ol style="list-style-type: none"> <li>1. SOFA scores</li> <li>2. Duration of mechanical ventilation</li> <li>3. AKI</li> <li>4. ICU length of stay</li> <li>5. ICU mortality</li> </ol>	<p>Significant increase in</p> <ol style="list-style-type: none"> <li>1. 25-OHD concentration (<math>p &lt; 0.0001</math>)</li> </ol> <p>No significant difference in</p> <ol style="list-style-type: none"> <li>1. Markers of bone turnover (calcium, PTH, phosphorus, FGF-23, osteocalcin, sALP, B-crosslaps)</li> <li>2. Inflammation markers (CRP, WBC, LL-37, sCD163)</li> <li>3. Leukocyte function</li> </ol>
<p><b>Effect of Oral Versus Intramuscular Vitamin D Replacement on Oxidative Stress and Outcomes in Traumatic Mechanical Ventilated Patients Admitted to Intensive Care Unit (2020)</b></p> <p>Hasanloei M, PMID: 31486158</p>	<p>Randomized controlled clinical trial</p>	<p>72 critically ill patients with traumatic injury and vit D 10-30 ng/mL</p>	<p>Group 1: 50,000IU vitamin D3 daily for 6 days</p> <p>Group 2: 300,000IU i.m. vitamin D3 single dose</p> <p>Group 3: control</p>	<p>Statistically significant decrease in</p> <ol style="list-style-type: none"> <li>1. ICU length of stay (<math>p &lt; 0.05</math>)</li> <li>2. Duration of mechanical ventilation (<math>p &lt; 0.001</math>)</li> <li>3. SOFA scores (<math>p = 0.009</math>)</li> </ol> <p>No significant difference in</p> <ol style="list-style-type: none"> <li>1. Mortality</li> </ol>	<p>Significant increase in serum vitamin D3 (<math>p &lt; 0.001</math>)</p>

**Table S14: Vitamin D in critically ill patients: Currently ongoing trials**

Patient population	Estimated enrollment	Primary Aim	Study Design	Trial Identifier
<b>Critically ill patients</b>	240 patients	To compare the effects of three different supplementation doses of enteral vitamin D on mortality within 30 days	Randomized double-blind placebo controlled parallel group trial	NCT05937789
<b>Critically ill patients undergoing CRRT</b>	138 patients	To compare the effects of two different supplementation doses of enteral vitamin D3 on plasma levels, mortality, ICU LOS, SOFA scores and catecholamine administration.	Randomized clinical trial	NCT05657678
<b>Critically ill trauma patients</b>	100 patients	To compare the effects of high dose enteral vitamin D with placebo on ICU mortality	Randomized placebo-controlled trial	NCT05449522
<b>Critically ill patients</b>	60 patients	To compare enteral vitamin D supplementation with no supplementation on vitamin D blood levels, 30-day survival and 90-	Multicenter randomized clinical trial	NCT04292873

		day survival		
<b>Critically ill children</b>	766 patients	To evaluate the impact of rapid normalization of vitamin D status on new or progressive multi-organ dysfunction	Multicenter randomized double-blind controlled trial	NCT03742505
<b>Critically ill patients</b>	2400 patients	To evaluate the effects of high-dose vitamin D3 on 28-day mortality	Multicenter randomized double-blind controlled trial	NCT03188796



## VITAMIN E

**Table S15: Vitamin E in critically ill patients: Observational studies**

Study	Study design	Patient population	Results	Conclusion
<p><b>Plasma antioxidant status in septic critically ill patients: a decrease over time (2008)</b></p> <p>Doise JM, PMID: 18353115</p>	Case-control study	56 consecutive septic patients (septic shock n = 37, severe sepsis n = 19) and six healthy volunteers	<ol style="list-style-type: none"> <li>1. At the onset, there was no difference between the three groups in terms of total plasma antioxidant capacity (TAC) values</li> <li>2. Then, an equivalent time decline was observed in the two septic populations whatever the severity</li> <li>3. TAC was statistically linked to uric acid, proteins in particular albumin and bilirubin (multivariate analysis), but no correlation was found with any vitamin (A, C and E)</li> </ol> <p>A sharp and persistent decrease in vitamin C concentrations was underlined</p>	<ol style="list-style-type: none"> <li>1. TAC, unaffected at first, deteriorated over time whatever the severity of the infection in these critically ill patients. TAC, unable to distinguish severe sepsis and septic shock, is unlikely to be a particularly useful outcome measure</li> </ol>
<p><b>Inflammation, vitamin deficiencies and organ failure in critically ill patients (2009)</b></p> <p>Corcoran TB, PMID: 19775037</p>	Nested cohort study	98 patients admitted as emergencies to the intensive care unit, who had a stay of greater than 48 hours	<ol style="list-style-type: none"> <li>1. Vitamin E deficiency incidence ranging 27-42% on admission to ICU while another 6% developed it during ICU stay</li> <li>2. Vitamin B12 concentration was weakly associated with C-reactive protein concentrations on admission to the ICU (<math>p=0.002</math>) and with the Sequential Organ Failure Assessment score (<math>p=0.02</math>)</li> <li>3. Vitamin A concentration was weakly associated with the C-reactive protein concentrations on days one (<math>p=0.001</math>) and five (<math>p=0.03</math>)</li> <li>4. Change in deficiency status of any of the vitamins over time in the first week of ICU admission did not appear to influence mortality</li> </ol>	While weak correlations were identified between vitamins A and B12 and C-reactive protein and Sequential Organ Failure Assessment scores, the importance of these associations and their relationship to hospital mortality remain to be determined
<p><b>Markers of Oxidative Stress and Clinical Outcome in Critically ill Septic Patients: A Preliminary Study from North India (2016)</b></p>	Non-interventional clinical case-control study	<p>46 consecutive non-pediatric patients admitted to ICU with sepsis</p> <p>20 age and sex matched healthy subjects</p>	<ol style="list-style-type: none"> <li>1. Mean levels of malondialdehyde were higher in patients than controls (<math>p&lt;0.001</math>)</li> <li>2. Levels of alpha-tocopherol were lower in the patient group (<math>p&lt;0.001</math>)</li> <li>3. Mean APACHE II and ODIN scores were two to three-fold higher in non-survivor patients (<math>n=22</math>) in comparison with survivors (<math>n=18</math>) (<math>p&lt;0.001</math>)</li> <li>4. There was no significant difference between the two groups in</li> </ol>	<ol style="list-style-type: none"> <li>1. The oxidants in septic patients were significantly higher while antioxidants were significantly lower than healthy controls</li> <li>2. There was also a significant correlation with APACHE II and ODIN scores</li> <li>3. A large patient population-based study may draw more specific conclusions.</li> </ol>

Daga MK, PMID: 27656484		served as controls.	oxidants and antioxidants levels (p>0.05) 5. A significant and positive correlation was observed between oxidant -antioxidant levels and APACHE II, ODIN and International Normalized Ratio (INR) scores in septic patients overall	
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**Table S16: Vitamin E in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<b>Antioxidant therapy in the prevention of organ dysfunction syndrome and infectious complications after trauma: early results of a prospective randomized study (1999)</b>  Porter JM, PMID: 10231223	Prospective randomized controlled study	18 critically ill trauma patients	Antioxidant group where they received N-acetylcysteine, selenium, and vitamins C and E (IV selenium 50 mg/6h, PO/NG Vit E 400 IU/ 8 h, PO/NG Vit C 100 mg/8 h and PO/NG NAC 8 g/6 h Vs placebo for 7 days	Intervention group showed: 1. Fewer infectious complications 2. Fewer organ dysfunction  There were no deaths in either group	None
<b>Enteral feeding with a solution enriched with antioxidant vitamins A, C, and E enhances the resistance to oxidative stress (2000)</b>  Preiser JC, PMID: 11153621	Single-center, Prospective, randomized, double-blinded, placebo-controlled study	37 critically ill patients expected to require at least 7 days of enteral feeding	Formula supplemented with vitamins A (67 microg/dL), C (13.3 mg/ dL), and E (4.94 mg/dL), Vs an isocaloric and isonitrogenous control solution	No significant difference in clinical outcome	Intervention group showed: 1. Significantly increased concentrations of plasma beta-carotene (p < 0.01) and plasma and LDL-bound alpha-tocopherol (p < 0.05) Improved LDL resistance to oxidative stress (p < 0.05)
<b>Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: a placebo-controlled trial (2001)</b>  Berger MM, PMID:	Prospective, placebo-controlled randomised supplementation trial	31 critically ill trauma patients	Selenium only (IV for 5 days: 500 mcg/d) Vs Selenium + alpha-tocopherol+Zn (Se: 500 mcg, Alpha-tocopherol: 150 mg/d, Zn: 13 mg/d, all IV for 5 days) Vs placebo for 5 days	No signs of toxicity No difference in clinical outcome	1. Faster correction of FT4 after Se supplementation (p=0.04)

11280679					
<p><b>Influence of early trace element and vitamin E supplements on antioxidant status after major trauma: a controlled trial (2001)</b></p> <p>Berger MM, DOI: <a href="https://doi.org/10.1016/S0271-5317(00)00296-7">https://doi.org/10.1016/S0271-5317(00)00296-7</a></p>	Randomised controlled study	32 critically ill trauma patients with ISS >15	Selenium only (IV for 5 days: 500 mcg/d) Vs Selenium + Alpha-tocopherol +Zn+Cu (Se: 500 mcg, Alpha-tocopherol: 150 mg/d, Zn: 13 mg/d and Cu 2.6mg, all IV for 5 days) Vs placebo for 5 days	<p>Non-statistically significant lower MV duration and ICU length of stay in Se plus (p =0.15)</p> <p>1. No difference in rates of infection, hospital length of stay</p>	1. None
<p><b>Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients (2002)</b></p> <p>Nathens AB, PMID: 12454520</p>	Randomized, prospective study	595 critically ill surgical patients	Enteral tocopherol 1,000 IU q8h and IV ascorbic acid 1g Vs standard care	<p>In the intervention group:</p> <p>1. RR of pulmonary morbidity was 0.81</p> <p>2. Multiple organ failure was significantly less likely to occur with a relative risk of 0.43</p> <p>3. Shorter duration of mechanical ventilation</p> <p>Shorter length of ICU stay</p>	2. None
<p><b>The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial (2004)</b></p>	Prospective, randomized, double-blind, placebo-controlled trial	216 critically ill patients who enquired at least 10 days of enteral feeding with standard isocaloric and isonitrogenous dietetic feeding preparation	Supplementation with vitamins C (500 mg/d) and E (400 IU/d) Vs isotonic saline solution in the controls	<p>Intervention group showed</p> <p>1. Significant reduction in 28-day mortality</p> <p>2. Significant reduction in duration of mechanical ventilation</p> <p>3. Significant reduction in the number of ventilator-free days</p> <p>No difference in rates of ARDS, MOF, infections and hospital length of stay</p>	<p>1. Plasma lipoperoxidation (by thiobarbituric acid reactive substances [TBARS] and prostaglandin F(2alpha) isoprostane levels) were significantly improved by the administration of antioxidants (AOX) (p&lt; 0.01 for both)</p> <p>2. AOX significantly increased the concentration of plasma and LDL-bound vitamin E (p &lt; 0.01)</p> <p>3. AOX improved LDL resistance to</p>

					oxidative stress by approximately 30% (P< 0.04) 3. Plasma levels of vitamin E were inversely correlated with the duration of mechanical ventilation in the AOX-treated patients (P< 0.05)
Crimi E, PMID: 15333422					
<b>Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury (2006)</b>	Single-center, prospective, randomized, controlled, unblinded study	100 patients with acute lung injury, diagnosed according to the American-European Consensus Conference on ARDS	Enteral supplementation of Eicosapentanoic acid (EPA) and gamma-linolenic acid (GLA) and vitamins A, C and E (317 IU/L vs 47.6 IU/L) Vs standard isonitrogenous, isocaloric enteral diet for 14 days	Intervention group showed: Significantly lower length of ventilation (p < 0.04)  No difference in survival	Intervention group showed: 1. Significant improvement in oxygenation (p < 0.05) 2. Significant higher compliance at day 7 (p < 0.05) No significant difference was found in nutritional variables Significantly higher resting energy expenditure (p < 0.05)
Singer P, PMID: 16484911					
<b>Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock (2006)</b>	Prospective, double-blind, placebo-controlled, randomized trial	165 critically ill patients with severe sepsis or septic shock, ARDS requiring MV, PFR<200	Continuously tube-fed with either a diet enriched with EPA, GLA, and elevated antioxidants or an isonitrogenous and isocaloric control diet, delivered at a constant rate to achieve a minimum of 75% of basal energy expenditure x 1.3 during a minimum of 4 days (Vit E 320 vs control 65 IU/L)	Intervention group showed: 1. Significant reduction in mortality rate (p=0.037) 2. More ventilator-free days (p < .001) 3. More intensive care unit (ICU)-free days (p < .001) Lesser development of new organ dysfunctions (p < .001)	Intervention group showed: Significant improvement in oxygenation status
Pontes-Arruda A, PMID: 16850002					
<b>A diet enriched in eicosapentanoic acid, gamma-linolenic acid and antioxidants in the</b>	Randomized, prospective, controlled study	100 critically ill patients with acute lung injury (ALI)	Enteral supplementation of eicosapentanoic acid (EPA) and gamma-linolenic acid (GLA) and vitamins A, C and E (317	Intervention group showed: 1. Significantly lower rate of occurrence of new pressure ulcers (p<0.05)	There was no significant difference in the nutritional parameters between the two groups

<p><b>prevention of new pressure ulcer formation in critically ill patients with acute lung injury: A randomized, prospective, controlled study (2007)</b></p> <p>Theilla M, PMID: 17933438</p>			<p>IU/L vs 85 IU/L) Vs a diet matched with macronutrients only</p>	<p>No difference was observed in the healing of existing pressure ulcers</p>	
<p><b>Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial (2008)</b></p> <p>Beale RJ, PMID: 18007263</p>	<p>Single-center, prospective, randomized, controlled, double-blind clinical trial</p>	<p>Fifty-five critically ill, septic patients requiring enteral feeding (patients showing inflammatory response with single organ failure)</p>	<p>Enteral supplement (500 mL of Intestamin, Fresenius Kabi) containing conditionally essential nutrients or a control solution via the nasogastric route for up to 10 days (Vit E 513 mg vs 13 mg per 1.5 L feed)</p>	<p>No differences in mortality at ICU or hospital discharge, 28 days, and 6 months or in ICU and hospital LOS</p>	<p>Intervention group showed:</p> <ol style="list-style-type: none"> <li>1. Significantly faster decline in the regression slopes of delta daily total SOFA score (<math>p &lt; 0.0001</math>)</li> <li>2. Vitamin C, as a marker of supplement absorption, increased by day 3 (<math>p = 0.002</math>)</li> </ol> <p>Significant increase in serum glycine, serine, arginine, ornithine, vitamin E, and beta-carotene</p>
<p><b>Influence of early antioxidant supplements on clinical evolution and organ function in critically ill cardiac surgery, major trauma, and subarachnoid hemorrhage patients (2008)</b></p> <p>Berger MM, PMID: 18687132</p>	<p>Prospective, randomized, double-blind, placebo-controlled, single-center trial</p>	<p>200 critically ill patients with conditions characterised by oxidative stress (organ failure after complicated cardiac surgery, major trauma, or subarachnoid hemorrhage)</p>	<p>Antioxidants (AOX) for 5 days (IV selenium 270 micg, zinc 30 mg, vitamin C 1.1 g, and vitamin B1 100 mg) with a double-loading dose on days 1 and 2 or placebo</p>	<ul style="list-style-type: none"> <li>• Significantly shorter hospital length of stay in surviving AOX trauma patients (<math>P = 0.045</math>)</li> <li>• No difference in <ol style="list-style-type: none"> <li>1. Organ function endpoints</li> <li>2. Infectious complications</li> </ol> </li> <li>• Similar incidence of acute kidney failure</li> </ul> <p>Similar reductions in sequential organ failure assessment score (SOFA)</p>	<ul style="list-style-type: none"> <li>• Plasma concentrations of selenium, zinc, and glutathione peroxidase, low on admission, increased significantly to within normal values in the AOX group</li> </ul> <p>C-reactive protein decreased faster in the AOX group (<math>p = 0.039</math>).</p>
<p><b>Effects of vitamin E</b></p>	<p>Randomised</p>	<p>20 critically ill</p>			<p>Vitamin E group showed</p>

<p><b>administration on APACHE II Score in ARDS patients (2009)</b></p> <p>Hajimahmoodi M, DOI: <a href="http://daru.tums.ac.ir/index.php/daru/article/view/516">http://daru.tums.ac.ir/index.php/daru/article/view/516</a></p>	<p>controlled trial</p>	<p>patients with ARDS</p>			<ol style="list-style-type: none"> <li>1. Better APACHE II score from day 2</li> <li>2. Higher Vit E concentration</li> </ol>
<p><b>The Relationship Between Vitamin E Plasma and BAL Concentrations, SOD Activity and Ventilatory Support Measures in Critically Ill Patients (2011)</b></p> <p>Ziaie S, PMID: 24250434</p>	<p>Prospective randomised controlled trial</p>	<p>25 mechanically ventilated ICU patients (<math>\geq 72</math> h on mechanical ventilation + <math>FiO_2 &gt; 50\%</math> and <math>PEEP &gt; 5</math> cm H<sub>2</sub>O)</p>	<p>3 IM doses (1000 IU each) of vitamin E Vs placebo for 3 days</p>	<p>None</p>	<p>Intervention group showed</p> <ol style="list-style-type: none"> <li>1. Significant differences in plasma and BAL vitamin E concentrations (<math>p = 0.01</math>)</li> <li>2. Non-significant decrease in SOD activities (Plasma <math>p = 0.23</math> and BAL <math>p = 0.016</math>)</li> <li>3. Progressive reduction in Acute Physiology and Chronic Health Evaluation II (APACHE II) (<math>p = 0.52</math>)</li> <li>4. Progressive reduction in Sequential Organ Failure Assessment (SOFA) (<math>p = 0.008</math>) score</li> </ol>
<p><b>Administration of vitamin C and vitamin E in severe head injury: a randomized double-blind controlled trial (2011)</b></p>	<p>Randomised, double-blind controlled trial</p>	<p>100 adult patients (age <math>\geq 16</math> years) with severe head injury, as defined by a Glasgow Coma Scale score of <math>\leq 8</math>, with the radiologic</p>	<p>Group A: vitamin C 500 mg/d IV for 7 days Group B: vitamin C 10 g IV on the first and fourth days followed by 4 g/d IV for 3 days Group C: vitamin E (400 IU/d IM) for 7 days Group D: placebo.</p>	<ol style="list-style-type: none"> <li>2. Vitamin E group showed a significantly lower rate of mortality than the other groups (<math>p = 0.04</math>) The GOS scores at discharge and follow-up were also significantly better for the vitamin E group patients (<math>p = 0.04</math>)</li> </ol>	<ol style="list-style-type: none"> <li>4. High-dose vitamin C stabilized or reduced the diameter of perilesional hypodense region significantly (<math>p = 0.01</math>)</li> <li>5. No other significant trend seen in size of hematoma (<math>p = 0.1</math>), appearance of basal cisterns (<math>p = 0.82</math>), and midline shift</li> </ol>

Razmkon A, PMID: 21916138		diagnosis of diffuse axonal injury			(p=0.36) No adverse effects related the dosing observed
<b>Effects of supplementation of antioxidant vitamins and lipid peroxidation in critically ill patients (2013)</b>  Nogueira CR, PMID: 24160231	Randomised controlled trial	23 critically ill patients	Diet with daily supplementation of 10,000 IU of vitamin A, 400 mg of vitamin E and 600 mg of vitamin C Vs standard diet	No significant difference regarding the clinical parameters	Serum concentrations vitamin C was higher after intervention in the intervention group
<b>A randomized trial of glutamine and antioxidants in critically ill patients (2013) [REDOXS Study]</b>  Heyland D, PMID: 23594003	Randomised controlled blinded 2-by-2 factorial trial	1223 critically ill adults with multiorgan failure and were receiving mechanical ventilation	Glutamine (0.35 g/kg/IBW per day intravenously according to ideal body weight and 30 g of glutamine, per day given enterally), antioxidants (500µg of selenium IV plus enteral 300 µg of selenium, 20 mg of zinc, 10 mg of beta carotene, 500 mg of vitamin E, and 1500 mg of vitamin C, both glutamine and antioxidants or placebo (IV and enteral)	<ul style="list-style-type: none"> <li>• There was a trend toward increased mortality at 28 days among patients who received glutamine as compared with those who did not receive glutamine (p=0.05)</li> <li>• In-hospital mortality and mortality at 6 months were significantly higher among those who received glutamine than among those who did not</li> <li>• Glutamine had no effect on rates of organ failure or infectious complications</li> <li>• Antioxidants had no effect on 28-day mortality (p=0.48) or any other secondary end point</li> </ul> No differences in serious adverse events (p=0.83)	None
<b>High-protein enteral nutrition enriched with</b>	Randomized, controlled,	301 adult critically ill	High-protein enteral nutrition enriched with immune-modulating	Higher 6-month mortality rate in the medical subgroup in the	None

<p><b>immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial (2014) [MetaPlus Study]</b></p> <p>Van Zanten ARH, PMID: 25096691</p>	<p>double-blind, multicenter trial</p>	<p>patients who were expected to be ventilated for more than 72 hours and to require enteral nutrition for more than 72 hours</p>	<p>nutrients (IMHP) containing glutamine, vitamin C and E, selenium, zinc and EPA + DHA, and low in carbohydrate content, vs standard high-protein (HP) enteral nutrition, initiated within 48 hours of ICU admission and continued during the ICU stay for a maximum of 28 days</p>	<p>IMHP group vs 35% in the HP group (p=0.04)</p> <p>No statistically significant differences in incidence of new infections</p>	
<p><b>Mechanical Ventilation Antioxidant Trial (2015)</b></p> <p>Howe KP, PMID: 26330437</p>	<p>Randomized, prospective, placebo-controlled double-blind design</p>	<p>Critically ill patients on mechanical ventilation (MV) for &gt;72 hours</p>	<p>Vitamin C 1000 mg plus vitamin E 1000 IU Vs vitamin C 1000 mg plus vitamin E 1000 IU plus N-acetylcysteine 400 mg Vs placebo solution as a bolus injection via their enteral feeding tube every 8 hours, for 28 days or till weaning from MV</p>	<p>No difference in all-cause mortality during hospitalization, ICU LOS, and hospital LOS</p>	<p>None</p>
<p><b>Effect of enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with sepsis-induced acute respiratory distress syndrome (2015)</b></p> <p>Shirai K, PMID: 26015869</p>	<p>Single-center, prospective, randomized, single-blind, controlled trial</p>	<p>46 critically ill patients with sepsis-induced ARDS on mechanical ventilation</p>	<p>Continuous EPA, GLA, and antioxidant-enriched diet Vs an isocaloric standard diet (including Vit E 210 vs control 45 mg/L of feed)</p>	<p>Intervention group showed: Significantly shorter ICU stay (p=0.008)</p> <p>No difference in the duration of mechanical ventilation, incidence of new nosocomial infections, changes over time in Sequential Organ Failure Assessment (SOFA) scores, and 60-day mortality</p>	<p>The ratio of partial pressure of oxygen to fraction of inspired oxygen on day 7 was significantly higher in the study group (p=0.021)</p>
<p><b>Effect of vitamin C and vitamin E on lung contusion: A randomized clinical trial study (2018)</b></p>	<p>Randomized, double-blind, placebo-controlled clinical trial</p>	<p>80 patients with injury severity score (ISS) 18 ± 2 due to blunt chest trauma</p>	<p>48 hours supplementation of IV vitamin E (1000 IU), IV vitamin C (500 mg), combined therapy with vitamin C (500 mg) and vitamin E (1000 IU) and control group (IV distilled water)</p>	<p>Combined therapy group showed significant decrease in ICU stay compared to other groups (p &lt; 0.001)</p>	<p>Combined therapy group showed:</p> <ol style="list-style-type: none"> <li>2. Significant increases pH, oxygen pressure, and oxygen saturation compared to other groups (p &lt; 0.001)</li> <li>3. Significant decrease in carbon dioxide pressure compared to</li> </ol>



Abdoulhossein D, PMID: 30479762					other groups ( $p < 0.001$ ) There was no significant difference cortisol and CRP levels between groups
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**Table S17: Vitamin E in critically ill patients: Currently ongoing trials**

Patient population	Estimated enrollment	Primary Aim	Study Design	Trial Identifier
<p><b>ICU patients with renal failure requiring Continuous Renal Replacement Therapy (CRRT)</b></p> <p><i>(The Effect of Vitamin E-coated Polysulfone Membrane on Oxidative Stress, Inflammation and Monocytes in Critically Ill Patients in CRRT)</i></p>	60	In vivo comparison of ROS concentrations in two groups (Copper, Zinc, superoxide dismutase, Endogenous peroxidase activity, Nitric Oxide, IL-6, IL-10,	<p>RCT (parallel assignment)</p> <p><u>Experimental:</u> RRT using ViE15-A hemofilter</p> <p><u>Active Comparator:</u> RRT using REXEED-15A</p>	NCT03489759
<p><b>Septic shock</b></p> <p><i>(Clinical Trial of Antioxidant Therapy in Patients with Septic Shock)</i></p>	131	<p>1. Parameters of oxidative stress: nitrates and nitrites, lipid peroxidation, glutathione peroxidase, glutathione s transferase, extracellular activity of SOD, GSH concentration and evaluation of total antioxidant capacity.</p> <p>2. Clinical outcomes: SOFA score</p>	<p>RCT</p> <p><u>Intervention:</u> Melatonin 50mg daily, 5 days Vitamin C 1g every 6hrs, 5 days Vitamin E 400 UNT every 8hrs, 5 days N-acetylcysteine 1200mg, every 12hrs, 5 days</p> <p><u>Control:</u> No intervention</p>	NCT03557229

## COPPER

**Table S18: Copper in critically ill population: Observational studies**

Study	Study design	Patient population	Results	Conclusion
<p><b>Trace minerals in critically ill patients: a forgotten cause of delayed recovery? (2004)</b></p> <p>Van der Hoven B, DOI: <a href="https://ccforum.biom">https://ccforum.biom</a></p>	<p>Prospective, observational pilot study in a surgical ICU of a tertiary referral centre</p>	<p>48 intensive care patients with two or more organ failures were included in the study (APACHE II score <math>24.2 \pm 7.9</math>)</p>	<ul style="list-style-type: none"> <li>• The overall daily caloric intake in the week before inclusion into the study was <math>1693 \pm 841</math> kcal and during the study period <math>2211 \pm 543</math> kcal (<math>P = 0.002</math>)</li> <li>• Copper levels at the start were normal (<math>14.5 \pm 6.3</math> <math>\mu\text{mol/l}</math>) and could be raised significantly (<math>17.4 \pm 4.6</math> <math>\mu\text{mol/l}</math>, <math>P = 0.004</math>)</li> <li>• Ceruloplasmin levels were within the normal range and did not change significantly over the study period (<math>0.34 \pm 0.11</math> g/l, <math>P = 0.414</math>)</li> <li>• Normal manganese levels at the start (<math>30.5 \pm 13.7</math> nmol/l) and were raised significantly (<math>37.0 \pm 16.3</math> nmol/l, <math>P = 0.021</math>)</li> <li>• (Very) low baseline levels were found in selenium (<math>0.53 \pm 0.22</math> <math>\mu\text{mol/l}</math>) and the supplement, although double the DRD, could not normalize this (<math>0.71 \pm 0.28</math> <math>\mu\text{mol/l}</math>), but the improvement was statistically significant (<math>P &lt; 0.0001</math>)</li> <li>• Albumin as the transport protein for selenium was low and did not change significantly (<math>20.9 \pm 6.0</math> g/l, <math>P = 0.959</math>)</li> <li>• Almost all patients were deficient at the start (<math>8.6 \pm 3.6</math> <math>\mu\text{mol/l}</math>, #), and</li> </ul>	<p>1. A significant percentage of ICU patients have trace mineral deficiencies, despite well-dosed parenteral (and/or enteral) feeding regimens</p> <p>Low plasma levels are not unequivocal to interpret but these results support a more prominent role for research and re-evaluation of the current recommended nutrition standards for ICU patients</p>

<a href="https://edcentral.com/articles/10.1186/cc2731">edcentral.com/articles/10.1186/cc2731</a>			<p>then supplementation did result in significant improvement, but only just to normal levels (<math>11.4 \pm 2.6 \mu\text{mol/l}</math>, <math>P &lt; 0.0001</math>)</p> <ul style="list-style-type: none"> <li>Starting levels of chromium were high (<math>86 \pm 52 \text{ nmol/l}</math>) and were raised non-significantly (<math>90 \pm 45 \text{ nmol/l}</math>)</li> </ul> <p>The chromium-transporting protein transferrin was low and did not change significantly (<math>1.3 \pm 0.9 \text{ g/l}</math>, <math>P = 0.475</math>)</p>	
<p><b>Trace element intakes should be revisited in burn nutrition protocols: A cohort study (2018)</b></p> <p>Jafari P, PMID: 28455105</p>	<p>Observational study</p>	<p>15 adult patients burned <math>29 \pm 20\%</math> of body surface (TBSA) over 8 days after injury</p>	<ul style="list-style-type: none"> <li>For the majority of 12 trace elements, the highest losses were observed on day 1, and declined thereafter</li> <li>Despite Cu supplementation (<math>4.23 \text{ mg/day}</math>) serum levels remained below reference values</li> <li>Se supplements (<math>745 \mu\text{g/day}</math>) normalized and even increased serum levels to upper normal value</li> <li>Despite large supplements (Zn <math>67.5 \text{ mg/day}</math>), serum Zn values remained below reference range</li> <li>Large exudative losses of B, Br and Mg were found, as well as of Fe and I, with the latter being probably due to contamination</li> </ul>	<ol style="list-style-type: none"> <li>Current nutritional Cu, Se, Zn repletion protocols in major burn patients which were based on measured exudative losses should be revised to include higher Cu and lower Se doses, as well as planned Mg administration</li> <li>In burns <math>&lt;20\%</math> TBSA and for the other TEs the recommended parenteral nutrition trace element doses appear sufficient</li> </ol>
<p><b>Serum Concentrations of Trace Elements Zinc, Copper, Selenium, and Manganese in Critically Ill Patients (2019)</b></p> <p>Lee YH, PMID: 30047077</p>	<p>Observational study</p>	<p>167 critically ill patients</p>	<ul style="list-style-type: none"> <li>At the time of intensive care unit (ICU) admission, serum concentrations of zinc, selenium, copper, and manganese were lower than the normal values in 75.1, 1.8, 37.8, and 2.1% of patients, respectively</li> <li>Serum trace element concentrations measured on day 14 of ICU stay were higher than those measured at the time of ICU admission for zinc (<math>53.3 \rightarrow 80.7 \mu\text{g/L}</math>) and copper (<math>87.1 \rightarrow 102.3 \mu\text{g/L}</math>)</li> <li>Increased serum zinc and copper concentrations during ICU care were associated with a significantly lower mortality compared to decreased concentrations of zinc (15.6 vs. 83.3%, <math>p = 0.003</math>) and copper (5.6 vs. 50.0%, <math>p = 0.013</math>)</li> </ul>	<ol style="list-style-type: none"> <li>At the time of ICU admission, low serum levels of zinc and copper were observed</li> <li>Patients with increased serum concentrations of zinc and copper had significantly lower mortality.</li> </ol>

<p><b>Serum trace elements levels in patients transferred from the intensive care unit to wards (2021)</b></p> <p>Gundogan K, PMID: 34330469</p>	<p>Prospective observational study</p>	<p>Adult patients (≥18 years) who stayed in ICU more than 48 h and transferred to ward</p>	<ul style="list-style-type: none"> <li>• The median age was 60 (40-70) years with Acute Physiology and Chronic Health Evaluation II (APACHE II) score 15 (11-21)</li> <li>• The median C-Reactive Protein (CRP) level was 53.9 (24.8-116.0) mg/L at discharge</li> <li>• Median serum zinc (24.4 mcg/dl:14.2-38.7) and chromium (0.22 mcg/dl:0.17-0.34) levels were below reference values, while median copper (111.9 (73.0-152.5) mcg/dl) and selenium (54.8 (36.4-95.25) mcg/L) values were within ranges</li> <li>• Serum concentrations of chromium, zinc, and selenium were lower than the normal values in 98, 90, and 36% of patients, respectively</li> <li>• The 28-day ICU mortality were correlated with low serum selenium levels (p = 0.03)</li> </ul>	<ol style="list-style-type: none"> <li>1. Serum chromium and zinc levels were below reference values at discharge, but this finding was in context of inflammation</li> <li>4. Low serum selenium level observed in 36% was associated to 28-day ICU mortality.</li> </ol>
<p><b>Micronutrient deficiencies in critically ill patients receiving continuous renal replacement therapy (2022)</b></p> <p>Fah M, PMID: 35871932</p>	<p>Retrospective chart review using electronic medical records</p>	<p>106 patients at high malnutrition risk requiring intensive care unit (ICU) admission, with one or more of the following serum micronutrient levels checked: carnitine, copper, zinc, selenium, and vitamins B1, B6, B9, and C (Micronutrient deficiencies were defined as below the reference range and carnitine deficiencies were interpreted as an acyl to free carnitine ratio (ACFR) of &gt;0.4)</p>	<ul style="list-style-type: none"> <li>• 46% were exposed to CRRT</li> <li>• At least one micronutrient deficiency was reported in 90% of CRRT patients compared to 61% patients unexposed to CRRT (p = 0.002)</li> <li>• A greater percentage of copper (p &lt; 0.001) and carnitine (p &lt; 0.001) deficiencies were found among patients exposed to CRRT, while more zinc deficiencies were noted among non-CRRT patients (p = 0.001)</li> </ul>	<ol style="list-style-type: none"> <li>1. The vast majority of CRRT patients presented with micronutrient deficiencies</li> <li>2. Clinicians should have a heightened awareness of the risk for serum copper, carnitine, and vitamin B6 deficiencies among CRRT patients</li> <li>3. Further prospective and randomized-controlled trials are needed to better define this new category of malnutrition and test supplementation strategies to address and prevent these clinically-relevant deficiencies</li> </ol>
<p><b>Serum micronutrient levels in critically ill</b></p>	<p>Prospective observational</p>	<p>50 mixed adult medical and surgical ICU</p>	<ul style="list-style-type: none"> <li>• The median APACHE II score on ICU admission was high at 24.0 (6.0-33.0)</li> </ul>	<ol style="list-style-type: none"> <li>1. Serum vitamin C, selenium and zinc concentrations were below</li> </ol>

<p><b>patients receiving continuous renal replacement therapy: A prospective, observational study (2022)</b></p> <p>Gundogan K, PMID: 35383966</p>	<p>study</p>	<p>patients with acute kidney injury (AKI)</p>	<ul style="list-style-type: none"> <li>• The median days on CRRT was 2.0 (2.0-4.0) days</li> <li>• At baseline (within 10-15 minutes of CRRT initiation), serum vitamin C, selenium and zinc were below normal</li> <li>• Serum vitamin B6 levels at 72 hours on CRRT were significantly lower than at 24 hours (p = 0.011)</li> <li>• Serum vitamin C values fell significantly at 24 and 72 hours during CRRT (p = 0.030 and p = 0.001), respectively, and remained low 24 and 48 hours after CRRT was stopped (p = 0.021)</li> <li>• At baseline and during CRRT, 96% of participants had at least two or more micronutrient levels below the normal range</li> </ul>	<p>2. the normal range at baseline CRRT was associated with a significant further decrease in levels of vitamin C, selenium and zinc</p>
<p><b>Evaluation of the Relationship Between Aquaporin-1, Hepcidin, Zinc, Copper, and Iron Levels and Oxidative Stress in the Serum of Critically Ill Patients with COVID-19 (2022)</b></p> <p>Bayraktar N, PMID: 36001235</p>	<p>Prospective case-control study</p>	<p>90 adult patients with and without COVID-19</p>	<ul style="list-style-type: none"> <li>• When the COVID-19 patient and the control groups were compared, all studied parameters were found to be statistically significant (p &lt; 0.01)</li> <li>• Total oxidant status (TOS), oxidative stress index (OSI), and AQP-1, hepcidin, and Cu levels were increased in patients with COVID-19 compared to healthy people</li> <li>• Serum TAC, Zn, and Fe levels were found to be lower in the patient group than in the control group</li> <li>• Significant correlations were detected between the studied parameters in COVID-19 patients</li> </ul>	<p>1. Oxidative stress may play an important role in viral infection due to SARS-CoV-2</p> <p>2. Oxidative stress parameters as well as some trace elements at the onset of COVID-19 disease will provide a better triage in terms of disease severity</p>

**Table S19: Copper in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p data-bbox="188 268 483 459"><b>Reduction of nosocomial pneumonia after major burns by trace element supplementation: aggregation of two randomised trials (2006)</b></p> <p data-bbox="188 496 398 555">Berger MM, PMID: 17081282</p>	<p data-bbox="506 268 698 459">Two consecutive, randomised, double-blinded, supplementation studies</p>	<p data-bbox="721 268 967 523">Two homogeneous groups of 41 severely burned patients (20 placebo and 21 intervention) admitted to the burn centre of a university hospital, combined</p>	<p data-bbox="990 268 1229 555">Intravenous trace element supplements (copper 2.5 to 3.1 mg/day, selenium 315 to 380 mug/day, and zinc 26.2 to 31.4 mg/day) for 8 to 21 days versus placebo</p>	<ol data-bbox="1252 268 1637 783" style="list-style-type: none"> <li>1. Significant reduction in number of infections was observed in the supplemented patients, which decreased from 3.5 +/- 1.2 to 2.0 +/- 1.0 episodes per patient in placebo group (<math>p &lt; 0.001</math>)</li> <li>2. This was related to a reduction of nosocomial pneumonia, which occurred in 16 (80%) patients versus seven (33%) patients, respectively (<math>p &lt; 0.001</math>), and of ventilator-associated pneumonia from 13 to six episodes, respectively (<math>p = 0.023</math>)</li> </ol>	<p data-bbox="1659 268 2018 555">Plasma trace element concentrations and antioxidative capacity were significantly enhanced with normalisation of plasma selenium, zinc, and glutathione peroxidase concentrations in plasma and skin in the trace element-supplemented group</p>

## IRON

**Table S20: Iron in critically ill population: Observational studies**

Study	Study design	Patient population	Results	Conclusion
<b>Diagnostic accuracy of serum hepcidin for iron deficiency in critically ill patients with anemia (2010)</b>  Lasocki S, PMID: 20213069	Prospective observational study	51 patients suffering from anemia (hemoglobin <100 g/l) and expected to stay for more than 7 days in intensive care	<ul style="list-style-type: none"> <li>• Median hepcidin levels were 80.5 (0.05-548.3) and 526.6 (246.7-891.4) microg/l for iron deficiency (ID) and non-ID profiles, respectively</li> <li>• Onset of ID during the ICU stay led to a progressive decline in hepcidin levels</li> <li>• A persistent inflammatory profile remained associated with high hepcidin concentrations</li> </ul> The optimal threshold for serum hepcidin for ID diagnosis was at 129.5 microg/l [95% CI = (115.5-143.4)]	<ul style="list-style-type: none"> <li>• Hepcidin levels may be suppressed by ID even in case of inflammation</li> </ul> Serum hepcidin of 129.5 microg/l was the most accurate threshold for ID diagnosis in critically ill patients with anemia
<b>Iron deficiency diagnosed using hepcidin on critical care discharge is an independent risk factor for death and poor quality of life at one year: an observational prospective study on 1161 patients (2018)</b>  Lasocki S, PMID: 30463596	Post-hoc analysis of prospective FROG-ICU, multicentre, observational cohort study	1161 critically ill survivors followed up one year after intensive care unit discharge	<ul style="list-style-type: none"> <li>• Using hepcidin 37% patients had iron deficiency, compared to 6% using ferritin alone and 13% using the sTfR/log(ferritin) ratio</li> <li>• Iron deficiency diagnosed according to low hepcidin was an independent predictor of one-year mortality (OR 1.51 (1.10-2.08)) as was high sTfR/log ferritin ratio (OR = 1.95 (1.27-3.00)), but low ferritin was not</li> </ul> Severe ID, defined as hepcidin < 10 ng/l, was also an independent predictor of poor one-year physical recovery (1.58 (1.01-2.49))	Iron deficiency, diagnosed using hepcidin, is very frequent at intensive care unit discharge and is associated with increased one-year mortality and poorer physical recovery
<b>Serum hepcidin potentially identifies iron deficiency in survivors of critical illness at the time of</b>	Post-hoc analysis of RECOVER trial	117 critically ill ICU survivors at hospital discharge	<ul style="list-style-type: none"> <li>• Median serum hepcidin concentration was significantly lower in the iron deficiency and inflammation (IDI) group</li> <li>• No statistical difference in CRP concentrations</li> <li>• Levels of the sTfR-ferritin index were higher in the IDI group</li> <li>• sTfR-ferritin index showed a strong association with hepcidin (p&lt;</li> </ul>	<ul style="list-style-type: none"> <li>• High prevalence of anaemia at time of hospital discharge in ICU survivors</li> </ul> Up to one-third of inflamed



<p><b>hospital discharge (2018)</b></p> <p>Shah A, PMID: 29363744</p>			<p>0-001)</p> <ul style="list-style-type: none"> <li>No significant differences in age, illness severity, Hb and renal function between both groups</li> <li>The maximal Youden index was achieved at a hepcidin cut-off of &lt;19 ng/ml, with a sensitivity of 73% and specificity of 74%.</li> <li>11/110 patients would be considered eligible for oral iron replacement</li> <li>Applying a hepcidin cut-off &lt;19 ng/ml, a further 24 patients would be included, raising this to 32% of the anaemic cohort</li> </ul>	<p>and anaemic patients had a hepcidin level &lt;19 ng/ml, a cut-off with maximal sensitivity and specificity for identifying iron deficiency</p>
<p><b>Persistent inflammation and anemia among critically ill septic patients (2019)</b></p> <p>Loftus 2019, PMID: 30489504</p>	<p>Prospective observational cohort study</p>	<p>42 critically ill septic patients</p>	<ul style="list-style-type: none"> <li>Patients with negative AdjΔHb had significantly higher day 14 levels of IL-6 (<math>p &lt; 0.05</math>); IL-8 (<math>p = 0.01</math>); Granulocyte colony-stimulating factor (<math>p = 0.01</math>)</li> <li>Patients with lower AdjΔHb was associated with higher day 14 levels of IL-6 (<math>p &lt; 0.01</math>); IL-8 (<math>p = 0.04</math>); stromal cell-derived factor 1 (<math>p = 0.02</math>); tumor necrosis factor <math>\alpha</math> (<math>p = 0.02</math>)</li> <li>Patients with negative AdjΔHb had significantly lower mean corpuscular volume on days 4 (<math>p = 0.04</math>), 7 (<math>p = 0.04</math>), and 14 (<math>p = 0.03</math>) but similar serum transferrin receptor levels</li> <li>No association between negative or low AdjΔHb and EPO levels</li> </ul>	<p>Persistent elevation of inflammatory cytokines was associated with iron-restricted anemia among critically ill septic patients, occurring in the absence of systemic iron deficiency, independent of endogenous EPO</p>
<p><b>Potential of Parameters of Iron Metabolism for the Diagnosis of Anemia of Inflammation in the Critically Ill (2020)</b></p> <p>Boshuizen M, PMID: 32110195</p>	<p>Nested case-control study</p>	<p>30 critically ill patients developing anaemia of inflammation batched to 60 controls</p>	<ul style="list-style-type: none"> <li>Sensitivity of iron parameters for diagnosing AI ranged between 62-76%; Specificity of iron parameters for diagnosing AI ranged between 57-72%; Iron and transferrin show the greatest area under the curve</li> <li>Iron shows the highest sensitivity; Transferrin and transferrin saturation show the highest specificity; Hepcidin and ferritin show the lowest specificity</li> <li>At an actual anemia prevalence of 53%, the diagnostic accuracy of iron, transferrin, and transferrin saturation showed a positive predictive value of 71-73%</li> <li>Combining iron, transferrin, transferrin saturation, hepcidin, and/or ferritin levels did not increase the accuracy of the AI diagnosis</li> </ul>	<p>Low levels of commonly measured markers such as plasma iron, transferrin, and transferrin saturation have the highest sensitivity and specificity and outperform ferritin and hepcidin.</p>
<p><b>Prevalence of and</b></p>	<p>Population –</p>	<p>6901 adults (age</p>	<ul style="list-style-type: none"> <li>41% of the patients had anaemia preceding hospitalization;</li> </ul>	<p>Anaemia is common and often</p>

<p><b>Recovery from Anemia Following Hospitalization for Critical Illness Among Adults (2020)</b></p> <p>Warner MA, PMID: 32970158</p>	<p>based cohort study</p>	<p>≥18 years) admitted to intensive care</p>	<p>Haemoglobin values at hospital discharge were 10.8 g/Dl, with 80% having anaemia: 58% mild, 39% moderate, and 3% severe</p> <ul style="list-style-type: none"> <li>• Prevalence of anaemia post hospitalization was 56% at 3 months, 52% at 6 months, and 45% at 12 months</li> <li>• Rates of complete recovery from anaemia at 12 months were 58% for mild anaemia, 39% for moderate anaemia, and 24% for severe anaemia</li> <li>• Of those without baseline anaemia surviving hospitalization, 74% were anaemic at hospital discharge, with rates of complete 12-month recovery of 73% for mild anaemia, 62% for moderate anaemia, and 59% for severe anaemia</li> <li>• Higher hospital discharge haemoglobin concentrations were associated with decreased mortality (p = 0.02)</li> </ul>	<p>persistent in the first year after critical illness</p>
<p><b>Prevalence, management and outcomes associated with anaemia in ICU survivors: a retrospective study (2021)</b></p> <p>Shah A, PMID: 33789355</p>	<p>Retrospective cohort study</p>	<p>1174 ICU patients who survived to hospital discharge</p>	<ul style="list-style-type: none"> <li>• 53.3% patients had Hb &lt; 100 g.l-1 at ICU discharge</li> <li>• Of these, 46% had Hb &lt; 100 g.l-1 at hospital discharge compared with 27.2% who were discharged from ICU with Hb &gt; 100 g.l-1</li> <li>• 4.4% patients received oral iron before hospital discharge; One patient received intravenous iron and two received vitamin B12 and folate</li> <li>• Patients discharged from ICU with Hb &lt; 100 g.l-1 experienced a longer median post-ICU hospital length of stay (p = 0.0017)</li> <li>• Factors associated with Hb at hospital discharge were APACHE-2 score, ICU discharge Hb and ICU length of stay</li> </ul>	<p>High prevalence of anaemia at ICU discharge and subsequently hospital discharge; there is little active management of anaemia during this important time period; and Hb of &lt; 100 g.l-1 was associated with prolonged hospitalisation following ICU discharge</p>
<p><b>Association Between Iron Metabolism and Acute Kidney Injury in Critically Ill Patients with Diabetes (2022)</b></p>	<p>Retrospective observational study</p>	<p>4997 diabetic patients in ICU</p>	<ul style="list-style-type: none"> <li>• Independent risk factors for AKI in critical patients with diabetes <ul style="list-style-type: none"> <li>• Congestive heart failure (OR = 2.11)</li> <li>• Serum creatinine (OR = 1.342)</li> <li>• Oxford Acute Severity of Illness Score (OR = 1.075)</li> <li>• Increased SF (OR = 1.002)</li> <li>• Decreased transferrin (OR = 0.993)</li> </ul> </li> <li>• Independent risk factors for 6-month all-cause death in critical diabetic patients</li> </ul>	<p>Critically ill diabetic patients with AKI were easily complicated with abnormal iron metabolism Increase of SF is an important risk factor for AKI and all-cause death in critically ill patients with diabetes</p>

Mo M, PMID: 35574018			<ul style="list-style-type: none"> <li>Advanced age (OR = 1.031)</li> <li>AKI (OR = 1.197)</li> <li>Increased Sequential Organ Failure Assessment score (OR = 1.055)</li> <li>Increased serum ferritin (OR = 1.380)</li> <li>The AUROCs of SF and the regression model to predict AKI in critical patients with diabetes were 0.782 and 0.851, respectively</li> <li>The 6-month survival rate in SF-increased group was lower than that in SF-normal group (P &lt; 0.001)</li> </ul>	
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**Table S21: Iron in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<b>A multicenter, randomized clinical trial of IV iron supplementation for anaemia of traumatic critical illness (2014)</b>  Pieracci FM, PMID: 24797376	Multicenter, randomized, single-blind, placebo-controlled trial	Anaemic (haemoglobin < 12 g/dL) trauma patients enrolled within 72 hours of ICU admission and with an expected ICU length of stay of more than or equal to 5 days	IV iron sucrose 100 mg or placebo thrice weekly for up to 2 weeks	No significant difference between groups in the risk of infection, length of stay, or mortality	<ul style="list-style-type: none"> <li>Serum ferritin concentration increased significantly in the treatment arm on both day 7 (p &lt; 0.01) and day 14 (p &lt; 0.01)</li> <li>No significant difference between groups in transferrin saturation, erythrocyte zinc protoporphyrin concentration, haemoglobin concentration, or packed RBC transfusion requirement</li> </ul>
<b>Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial: A randomized trial of IV iron in critical illness</b>	Multicentre, randomized, placebo-controlled, blinded study	140 critically ill patients with ICU admission < 48 h before enrolment and Hb < 100 g/L at any time in the last 24 h	500 mg of IV ferric carboxymaltose; every 4 days, reassessment for a further dose, up to maximum 4 doses in total Vs matched	No significant difference in any safety outcome.	Median haemoglobin at hospital discharge was significantly higher in the intravenous iron group than in the placebo group (p = 0.02)

<p><b>(2016)</b></p> <p>Litton E, PMID: 27686346</p>			<p>placebo</p>		
<p><b>Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial (2020)</b></p> <p>Richards T, PMID: 32896294</p>	<p>Double-blind, parallel-group randomised trial</p>	<p>487 adult patients with anaemia (haemoglobin less than 130 g/L for men and 120 g/L for women) at preoperative hospital visits before elective major open abdominal surgery</p>	<p>IV iron as a single 1000 mg dose of ferric carboxymaltose in 100 mL normal saline Vs 100 mL normal saline, both given as an infusion over 15 min, 10-42 days preoperatively</p>	<p>No difference in death or any of the prespecified safety endpoints.</p>	<p>No difference in the need /rate of blood transfusion</p>
<p><b>Impact of treating iron deficiency, diagnosed according to hepcidin quantification, on outcomes after a prolonged ICU stay compared to standard care: a multicenter, randomized, single-blinded trial (2021)</b></p> <p>Lasocki S, PMID: 33588893</p>	<p>Multicenter, randomized, single-blinded trial</p>	<p>399 anaemic (WHO definition) critically ill patients with an ICU stay <math>\geq 5</math> days</p>	<p>IV iron (1 g of ferric carboxymaltose) when hepcidin was <math>&lt; 20\mu\text{g/l}</math> and with IV iron and erythropoietin for hepcidin levels 20-41<math>\mu\text{g/l}</math>. Control patients were treated according to standard care</p>	<ul style="list-style-type: none"> <li>• D90 mortality was significantly lower in intervention arm (<math>p = 0.008</math>)</li> <li>• one-year survival was improved (<math>p = 0.04</math>)</li> </ul>	<p>Number of days spent in hospital 90 days after ICU discharge (post-ICU LOS) was not different for intervention and control</p>
<p><b>Intravenous iron to treat anaemia following critical care: a multicentre feasibility randomised trial (2022)</b></p> <p>Shah A, PMID: 34872717</p>	<p>Multicentre, feasibility randomised controlled trial</p>	<p>98 critically ill patients discharged from the ICU with moderate or severe anaemia (haemoglobin <math>\leq 100</math> g L<sup>-1</sup>)</p>	<p>A single dose of IV ferric carboxymaltose 1000 mg Vs usual care</p>	<ul style="list-style-type: none"> <li>• Infection rates were similar in both groups</li> <li>• Hospital readmissions at 90 days post-ICU discharge were lower in the IV iron group (<math>p=0.037</math>)</li> <li>• Median post-ICU hospital stay was shorter in the IV iron group but did not show</li> </ul>	<p>IV iron resulted in a higher mean haemoglobin at 28 days and at 90 days (<math>P &lt; 0.001</math>)</p>

<p><b>Intravenous iron supplementation treats anemia and reduces blood transfusion requirements in patients undergoing coronary artery bypass grafting-A prospective randomized trial (2022)</b></p> <p>Shokri H, PMID: 35417958</p>	<p>Prospective randomized trial</p>	<p>80 preoperative coronary artery bypass grafting patients</p>	<p>A single IV dose of ferric carboxymaltose (1000 mg in 100 mL saline) infused slowly over 15 min 7 days before surgery Vs a single IV dose of saline (100 mL saline) infused slowly over 15 min 7 days before surgery</p>	<p>statistical significance</p> <ul style="list-style-type: none"> <li>• Iron therapy resulted in shorter hospital and ICU stay (P &lt; 0.001) and shorter aortic cross-clamp time</li> <li>• Incidence of postoperative complications was similar to the placebo group</li> </ul>	<ul style="list-style-type: none"> <li>• Lower incidence of anemia at 4 weeks after discharge (P &lt; 0.001)</li> <li>• Hb level was significantly higher in the iron group preoperatively and postoperatively, and 4 weeks after discharge (P &lt; 0.001).</li> <li>• Iron therapy resulted in reduced pRBCs requirements postoperatively</li> <li>• Percentage of reticulocytes was significantly higher in placebo group</li> </ul>
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## **SELENIUM**

**Table S22: Selenium in critically ill population: Interventional studies**

<b>Study</b>	<b>Level of evidence</b>	<b>Patient population</b>	<b>Intervention</b>	<b>Clinical endpoints</b>	<b>Surrogate endpoints</b>
<b>Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: a placebo-controlled trial (2001)</b>  Berger MM, PMID: 11280679	Prospective, placebo-controlled randomised supplementation trial	31 critically ill trauma patients with severe multiple injury (Injury Severity Score 30 +/- 7)	Supplementation during the first 5 days after injury with either Se Vs placebo (The selenium group was further randomised to receive daily 500 microg Se, with or without 150 mg alpha-tocopherol (AT) and 13 mg zinc supplements)	None	1. Plasma Se, low on D0, normalised from D1 in the selenium group  Total T4 and T3 increased more and faster after D2 (p=0.04 and 0.08), reverse T3 rising less between D0 and D2 (P=0.05)
<b>Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial (2003)</b>  Bertolini G, PMID: 12684745	Randomised multicentre unblinded controlled clinical trial	39 critically ill patients with severe sepsis or septic shock	Total parenteral nutrition or enteral nutrition, the latter containing extra L-arginine, omega-3 fatty acids, vitamin E, beta carotene, zinc, and selenium.	1. ICU mortality of patients with severe sepsis given enteral nutrition (EN) was higher than for those given PN (p=0.039)  More patients given EN than patients given PN still had severe sepsis when they died (p=0.055)	None
<b>Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis,</b>	Prospective randomized, placebo-controlled, multiple-center trial	92 patients with severe systemic inflammatory response syndrome, sepsis, and septic shock and an Acute Physiology and	1000 microg of IV sodium-selenite as a 30-min bolus injection, followed by 14 daily continuous infusions of 1000 microg intravenously Vs placebo	1. Significant reduction in 28-day mortality in the intervention group (p=0.049)  2. Mortality rate was significantly reduced in patients with septic shock	Whole blood selenium concentrations and glutathione peroxidase-3 activity were within the upper normal range during selenium treatment, whereas they

<p><b>and septic shock (2007)</b></p> <p>Angstwurm MWA, PMID: 17095947</p>		<p>Chronic Health Evaluation (APACHE) III score &gt;70</p>		<p>with disseminated intravascular coagulation (p=0.018) as well as in the most critically ill patients with an APACHE III score &gt; or =102 (p=0.040) or in patients with more than three organ dysfunctions (p=0.039)</p> <p>2. There were no side effects observed due to high-dose sodium-selenite treatment</p>	<p>remained significantly low in the placebo group</p>
<p><b>Effect of selenium supplementation on biochemical markers and outcome in critically ill patients (2007)</b></p> <p>Mishra V, PMID: 17174015</p>	<p>Prospective single-centre randomised controlled study</p>	<p>40 critically ill septic patients</p>	<p>high dose Selenium (474, 316, 158 microg/day), each for 3 consecutive days followed by a standard dose of 31.6 microg/day of Se (given as sodium selenite) Vs standard dose of Selenium</p>	<p>3. Requirement for renal replacement therapy was not significantly different between the groups</p>	<p>In the high dose selenium group</p> <p>1. Plasma Se increased by day 3 and 7 (P&lt;0.0001) and day 14 (P=0.02)</p> <p>2. Plasma GSH-Px increased by day 3 and 7 (P=0.01) Significant negative correlation between plasma Se and SOFA (sepsis related organ failure assessment) (p=0.03)</p>
<p><b>Influence of early antioxidant supplements on clinical evolution and organ function in critically ill cardiac surgery, major trauma, and subarachnoid hemorrhage patients (2008)</b></p>	<p>Prospective, randomized, double-blind, placebo-controlled, single-center trial</p>	<p>200 critically ill patients with organ failure after complicated cardiac surgery, major trauma, or subarachnoid hemorrhage</p>	<p>IV supplements (AOX) for 5 days (selenium 270 microg, zinc 30 mg, vitamin C 1.1 g, and vitamin B1 100 mg) with a double-loading dose on days 1 and 2 Vs placebo</p>	<p>1. Brain injury was more severe in the AOX trauma group (p= 0.019)</p> <p>2. Infectious complications, incidence of acute kidney injury, sequential organ</p>	<p>1. Plasma concentrations of selenium, zinc, and glutathione peroxidase, low on admission, increased significantly to within normal values in</p>

<p>Berger MM, PMID: 18687132</p>				<p>failure assessment (SOFA) score decrease, length of hospital stay, organ function endpoints did not differ</p> <p>4. Length of hospital stay was shorter only in surviving AOX trauma patients (p=0.045)</p>	<p>the AOX group C-reactive protein decreased faster in the AOX group (p=0.039)</p>
<p><b>High-dose selenium reduces ventilator-associated pneumonia and illness severity in critically ill patients with systemic inflammation (2011)</b></p> <p>Manzanares W, PMID: 21445641</p>	<p>Prospective, placebo-controlled, randomized, single-blinded phase II study</p>	<p>35 SIRS patients with a minimal Acute Physiology and Chronic Health Evaluation (APACHE) II score <math>\geq 15</math> and predicted mechanical ventilation (MV) for &gt;48 h</p>	<p>High-dose selenious acid in 0.9% sodium chloride solution [a bolus loading dose of 2,000 <math>\mu\text{g}</math> (25.30 <math>\mu\text{mol}</math>) Se over 2 h within 2 h after enrolment, and thereafter 1,600 <math>\mu\text{g}/\text{day}</math> (20.24 <math>\mu\text{mol}/\text{day}</math>) Se as a daily continuous infusion for 10 days (total dose of Se 18 mg, 227.7 <math>\mu\text{mol}</math>)] Vs placebo (Just NaCl) for 10 days</p>	<p>1. Early VAP rate was lower in the intervention group (p=0.04)</p> <p>2. Hospital-acquired pneumonia was lower after ICU discharge (p=0.03)</p> <p>1. No adverse events attributable to selenite were observed</p>	<p>1. SOFA score decreased significantly in the intervention group (p=0.0001)</p> <p>1. Glutathione peroxidase-3 (GPx-3) activity increased in both groups</p>
<p><b>Tolerability and efficacy of a low-volume enteral supplement containing key nutrients in the critically ill (2011)</b></p> <p>Schneider A, PMID: 21621886</p>	<p>Randomized, prospective, single-blind, controlled study</p>	<p>58 critically ill patients</p>	<p>Low-volume enteral supplement containing key nutrients Vs a diluted standard nutrition solution</p>	<p>1. No difference in clinical parameters such as fever, antibiotic treatment, artificial ventilation, and death</p> <p>3. No difference in ICU or hospital stay</p>	<p>2. The difference in vitamin E and selenium uptake was higher in the intervention group (p<math>\leq</math> 0.011)</p>
<p><b>Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for</b></p>	<p>Randomised, double blinded, factorial,</p>	<p>502 critically ill patients in ICU/HDU for <math>\geq</math> 48 hours, with</p>	<p>Parenteral glutamine (20.2 g/day) or selenium (500 <math>\mu\text{g}/\text{day}</math>), or both, for up to seven days.</p>	<p>Selenium or glutamine supplementation showed</p> <p>1. No significant effect on developing a new</p>	<p>1. None</p>



<p><b>critically ill patients (2011)</b></p> <p>Andrews PJ, PMID: 21415104</p>	<p>controlled trial</p>	<p>gastrointestinal failure and requiring parenteral nutrition</p>		<p>infection, length of stay, days of antibiotic use, or modified SOFA score</p> <p>1. No significant effect on 6-month mortality were</p>	
<p><b>High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial (2014) [MetaPlus Study]</b></p> <p>Van Zanten ARH, PMID: 25096691</p>	<p>Randomized, controlled, double-blind, multicenter trial</p>	<p>301 adult critically ill patients who were expected to be ventilated for more than 72 hours and to require enteral nutrition for more than 72 hours</p>	<p>High-protein enteral nutrition enriched with immune-modulating nutrients (IMHP) containing glutamine, vitamin C and E, selenium, zinc and EPA + DHA, and low in carbohydrate content, vs standard high-protein (HP) enteral nutrition, initiated within 48 hours of ICU admission and continued during the ICU stay for a maximum of 28 days</p>	<p>1. Higher 6-month mortality rate in the medical subgroup in the IMHP group vs 35% in the HP group (p=0.04)</p> <p>2. No statistically significant differences in incidence of new infections</p>	<p>None</p>
<p><b>Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial [Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT)] (2016)</b></p> <p>Bloos F, PMID: 27428731</p>	<p>Multicentre randomised controlled clinical trial</p>	<p>1089 patients with severe sepsis or septic shock</p>	<p>An initial intravenous loading dose of sodium selenite, 1000 µg, followed by a continuous intravenous infusion of sodium selenite, 1000 µg, daily until discharge from the intensive care unit, but not longer than 21 days, Vs placebo. Patients also were randomized to receive anti-infectious therapy guided by a procalcitonin algorithm or without procalcitonin guidance.</p>	<p>No statistically significant difference in</p> <ul style="list-style-type: none"> <li>• 28-day mortality rate (p = 0.3)</li> <li>• 28-day mortality between patients assigned to procalcitonin guidance (p =0.34)</li> <li>• 90-day all-cause mortality</li> <li>• Intervention-free days</li> <li>• Antimicrobial costs</li> <li>• Antimicrobial-free days</li> <li>• Secondary infections</li> </ul>	<p>Procalcitonin guidance</p> <ul style="list-style-type: none"> <li>• Did not affect frequency of diagnostic or therapeutic procedures</li> <li>• Resulted in a 4.5% reduction of antimicrobial exposure</li> </ul>
<p><b>Antioxidant reserve of the</b></p>	<p>Randomised</p>	<p>90 mechanically</p>	<p>IV selenium Vs isotonic</p>	<p>2. Non-significant reduction</p>	<p>Serum selenium and GPX-3</p>

<p><b>lungs and ventilator-associated pneumonia: A clinical trial of high dose selenium in critically ill patients (2018)</b></p> <p>Mahmoodpoor A, PMID: 29288963</p>	<p>controlled trial</p>	<p>ventilated patients</p>	<p>saline infusion for 10 days</p>	<p>in the incidence of VAP in the intervention group (p=0.250)</p> <p>The risk of VAP or death was similar between the intervention and placebo group</p>	<p>activity levels increased steadily in the intervention group (p&lt;0.025)</p>
<p><b>The Effect of Intravenous Selenium on Oxidative Stress in Critically Ill Patients with Acute Respiratory Distress Syndrome (2019)</b></p> <p>Mahmoodpoor A, PMID: 30001171</p>	<p>Randomized controlled trial</p>	<p>40 critically ill patients with ARDS</p>	<p>IV Sodium selenite Vs normal saline for 10 days</p>	<p>2. Significant improvement in airway resistance and pulmonary compliance changes in the intervention group (P=0.008 and p=0.028, respectively)</p> <p>No effect on the overall survival, the duration of mechanical ventilation, and ICU stay</p>	<p>2. Selenium concentrations were linearly correlated to serum concentrations of glutathione peroxidase-3 (GPX-3) (p&lt; 0.001), and FRAP (p&lt; 0.001)</p> <p>Serum concentrations of both IL 1-beta (p&lt; 0.001) and IL-6 (p&lt; 0.001) were inversely correlated to the serum concentrations of selenium</p>

## ZINC

**Table 23: Zinc in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p><b>Zinc supplementation is associated with improved neurologic recovery rate and visceral protein levels of patients with severe closed head injury (1996)</b></p> <p>Young B, PMID: 8714860</p>	Single-centre randomized, prospective, double-blinded controlled trial	68 adult patients with severe closed head injury, who were all receiving total parenteral nutrition	Pharmacological zinc supplementation (12 mg of zinc IV for 15 days followed by 22 mg of enteral zinc from day 15 to 3 months) - controls usual care (2.5 mg of zinc IV for 15 days followed by placebo from day 15 to 3 months)	<p>Zn supplementation group:</p> <ol style="list-style-type: none"> <li>1. Lower mortality rate at 1 month</li> <li>2. GCS scores exceeded the adjusted mean GCS score of the standard group at day 28 (<math>p = 0.03</math>)</li> </ol> <p>Mean motor GCS score levels were significantly higher on days 15, 21 and 28 (<math>p = 0.005</math>, <math>p = 0.02</math>, <math>p=0.09</math>)</p>	<ol style="list-style-type: none"> <li>1. The groups did not differ in serum zinc concentration, weight, energy expenditure, or total urinary nitrogen excretion after hospital admission</li> <li>2. Mean 24-h urine zinc levels were significantly higher in the zinc-supplemented group at days 2 (<math>p = 0.0001</math>) and 10 (<math>p = 0.01</math>) after injury</li> <li>3. Mean serum prealbumin concentrations were significantly higher in the zinc-supplemented group (<math>p = 0.003</math>) at 3 weeks after injury</li> <li>4. A similar pattern was found for mean serum retinol binding protein level (<math>p = 0.01</math>).</li> </ol>
<p><b>Impact of Zinc Supplementation on the Clinical Outcomes of Patients with Severe Head Trauma: A Double-Blind Randomized Clinical Trial (2018)</b></p> <p>Khazdouz M, PMID: 28467150</p>	Single-centre double blind randomised controlled trial	100 adult patients with severe head trauma	120 mg zinc daily via a nasogastric tube for 15 days Vs placebo	<p>Zn supplementation group:</p> <ol style="list-style-type: none"> <li>1. LOS was shorter (<math>p = 0.043</math>)</li> <li>2. Mortality rate on day 28 was borderline lower (<math>p = 0.507</math>)</li> </ol>	<p>Zn supplementation group:</p> <ol style="list-style-type: none"> <li>1. Mean plasma zinc concentration was significantly higher on day 7 (<math>p &lt; 0.001</math>) and day 16 (<math>p &lt; 0.001</math>)</li> <li>2. SOFA, GOS, and inflammation factors were significantly better by day 16 (all <math>p &lt; 0.05</math>)</li> </ol>

**Table S24: Zinc in critically ill patients: Currently ongoing trials**

Patient population	Estimated enrollment	Primary Aim	Study Design	Trial Identifier
<p><b>Zinc Therapy in Critical Illness</b></p> <p><i>(Pharmakonutrients as Therapies for Critical Illness: Zinc in Severe Sepsis)</i></p>	<p>55 mechanically ventilated patients with severe sepsis</p>	<ol style="list-style-type: none"> <li>1. To perform a phase I dose-finding study of intravenous zinc in mechanically ventilated patients with severe sepsis</li> <li>2. To define the pharmacokinetic of intravenous zinc in mechanically ventilated patients with severe sepsis compared to healthy controls</li> <li>3. To investigate the impact of zinc on inflammation, immunity, and oxidant defense in patients with severe sepsis.</li> </ol>	<ul style="list-style-type: none"> <li>• Single-centre RCT</li> <li>• 40 critically ill patients in sepsis on mechanical ventilation and 15 healthy volunteers.</li> <li>• 40 critically ill patients will be divided into 4 dosing groups of 10 subjects (7 randomized to zinc and 3 to saline placebo)</li> <li>• Group 1 will receive 500mcg/kg IBW/day elemental zinc in divided doses every 8 hours. If the 50th percentile of the normal plasma zinc range (110mcg/dL) has not been achieved in all patients by 7 days and there are no safety concerns, sequential groups of patients will receive increasing doses in 250mcg increments to the ceiling dose. Groups 2 through 4 will receive 750, 1000, and 1250mcg/kgIBW/day elemental zinc, respectively</li> <li>• Each participant will receive the intravenous zinc or placebo for a total of 7 days unless they die or leave the ICU earlier</li> </ul>	<p>NCT01162109</p>

## CARNITINE

**Table S25: Carnitine in critically ill population: Observational studies**

Study	Study design	Patient population	Results	Conclusion
<p><b>Septic Shock Nonsurvivors Have Persistently Elevated Acylcarnitines Following Carnitine Supplementation (2018)</b></p> <p>Puskarich MA, PMID: 29384504</p>	Retrospective observational study	31 patients with septic shock (data analysis from the 2014 RCT by same authors)	<ul style="list-style-type: none"> <li>• Mortality was 50% and 80% at 1 year for L-carnitine and placebo-treated patients, respectively</li> <li>• Free carnitine, C2, C3, and C8 acylcarnitines were higher among non-survivors at enrolment</li> <li>• L-Carnitine treatment increased levels of all measured acylcarnitines; an effect that was sustained for at least 36 h following completion of the infusion and was more prominent among non-survivors</li> <li>• Several fatty acids followed a similar, though less consistent pattern</li> <li>• Glucose, lactate, and insulin levels did not differ based on survival or treatment arm</li> </ul>	<p>In septic shock, L-Carnitine supplementation increases a broad range of acylcarnitine concentrations that persist after cessation of infusion, demonstrating both immediate and sustained effects on the serum metabolome</p> <p>Non-survivors demonstrate a distinct metabolic response to L-carnitine compared with survivors, which may indicate pre-existing or more profound metabolic derangement that constrains any beneficial response to treatment</p>
<p><b>Altered Serum Acylcarnitines Profile after a Prolonged Stay in Intensive Care (2022)</b></p> <p>Rousseau AF, PMID: 35268097</p>	Observational case-control study	162 survivors of a prolonged ICU stay ( $\geq 7$ days) compared with 50 non-hospitalised adults	<ul style="list-style-type: none"> <li>• Their acylcarnitines (AC) profile was significantly different compared to reference ranges (RR) from healthy subjects, mostly in terms of short chain AC (<math>p &lt; 0.001</math>)</li> <li>• Free carnitine (C0) concentration of survivors was similar to healthy subjects (<math>p = 0.55</math>)</li> <li>• C0 below percentile 2.5 of RR was observed in 6/162 (3.7%) survivors</li> <li>• Their total AC/C0 ratio was 0.33 (0.22–0.42).</li> </ul>	<p>In ICU survivors, carnitine deficiency was rare, but AC profile was altered and AC/C0 ratio was abnormal in more than 25%. The value of AC profile as a marker of post-ICU dysmetabolism needs further investigations.</p>

			A ratio above 0.4 was observed in 45/162 (27.8%) patients	
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**Table S26: Carnitine in critically ill population: Interventional studies**

Study	Level of evidence	Patient population	Intervention	Clinical endpoints	Surrogate endpoints
<p><b>Preliminary safety and efficacy of L-carnitine infusion for the treatment of vasopressor-dependent septic shock: a randomized control trial (2014)</b></p> <p>Puskarich MA, PMID: 23851424</p>	Double – blind andomised controlled trial	31 patients with vasopressor - dependant septic shock (cumulative vasopressor index $\geq 3$ and sequential organ failure assessment (SOFA) score $\geq 5$ within 16 hours of the recognition of septic shock)	Parenteral L-carnitine as a 4g bolus injection over 2–3 minutes followed by 8g infusion over the following 12 hours as compared to placebo (normal saline)	<ul style="list-style-type: none"> <li>• Mortality was significantly lower at 28 days in the L-carnitine group (<math>p = 0.048</math>)</li> <li>• Improved 1-year survival (<math>p= 0.06</math>)</li> <li>• No difference in SAEs between placebo and intervention</li> </ul>	No difference in the proportion of patients achieving a decrease in SOFA score of 2 or more points at 24 hours between placebo and treatment
<p><b>Effect of Levocarnitine vs Placebo as an Adjunctive Treatment for Septic Shock: The Rapid Administration of Carnitine in Sepsis (RACE) Randomized Clinical Trial (2018)</b></p> <p>Jones AE, PMID: 30646314</p>	Multi-center adaptive, randomized, blinded, dose-finding, phase 2 clinical trial	250 patients with vasopressor resistant septic shock and moderate organ failure	Low (6 g), medium (12 g), or high (18 g) doses of parenteral levocarnitine or an equivalent volume of saline placebo administered as a 12-hour infusion	No mortality benefit with any of the L-carnitine regime	<ul style="list-style-type: none"> <li>• Fitted mean (SD) changes in the SOFA score for the low, medium, and high levocarnitine groups were 1.27, 1.66, and 1.97, respectively, vs 1.63 in the placebo group</li> <li>• The posterior probability that the 18-g dose is superior to placebo was 0.78, which did not meet the a priori threshold of 0.90</li> </ul>
<p><b>A pilot trial of l-carnitine in patients with traumatic brain</b></p>	Randomised controlled trial	40 patients with severe TBI	2g/day of	<ul style="list-style-type: none"> <li>• Neurocognitive function</li> </ul>	No difference in Neuron Specific Enolase (NSE) levels between the

<p><b>injury: Effects on biomarkers of injury (2018)</b></p> <p>Mahmoodpoor A, PMID: 29454227</p>			<p>enteral L-carnitine, during the first ICU-week as compared to placebo.</p>	<p>significantly improved within one week in both groups</p> <ul style="list-style-type: none"> <li>Improved cerebral edema in carnitine group (p=0.044)</li> <li>No improvement in 90-day mortality (p = 0.76)</li> </ul>	<p>two groups</p>
<p><b>L-carnitine supplementation ameliorates insulin resistance in critically ill acute stroke patients: a randomized, double-blinded, placebo-controlled clinical trial (2022)</b></p> <p>Nejati M, PMID: 34909045</p>	<p>Randomized, double-blinded, placebo-controlled clinical trial</p>	<p>48 critically ill patients with ischaemic stroke</p>	<p>1.5g of oral L-carnitine provided over six days as compared to placebo for 6 days</p>	<p>No significant improvements in clinical outcomes</p>	<p>L-carnitine improved insulin resistance (improved HOMA-IR index)</p>
<p><b>The effects of L-Carnitine supplementation on inflammatory markers, clinical status, and 28 days mortality in critically ill patients: A double-blind, randomized, placebo-controlled trial (2022)</b></p> <p>Yahyapoor F, PMID: 35623869</p>	<p>Randomized, double-blind, placebo-controlled trial</p>	<p>51 critically ill adults</p>	<p>L-Carnitine (3g/day) enterally, and placebo for 7 days</p>	<p>None</p>	<ul style="list-style-type: none"> <li>L-carnitine significantly reduced the levels of CRP and IL-6 compared to the baseline, which is both statistically significant compared with the control group (p &lt; 0.05)</li> <li>The SOFA and APACHE scores were significantly reduced in the L-Carnitine group compared with the placebo group (p = 0.02 and p &lt; 0.001, respectively)</li> </ul>
<p><b>The effects of adjunctive treatment with L-carnitine on monitoring laboratory variables in ICU patients: a</b></p>	<p>Prospective, double-blind, randomized controlled trial</p>	<p>51 critically ill adults with multiple medical conditions</p>	<p>Enteral L-carnitine 3g/day as compared to placebo</p>	<p>None</p>	<ul style="list-style-type: none"> <li>Serum albumin (p=0.001), total protein (p= 0.003), and calcium (p=0.044) significantly increased with carnitine</li> </ul>

<p><b>double-blinded randomized controlled clinical trial (2023)</b></p> <p>Yahyapoor F, DOI: <a href="http://dx.doi.org/10.1186/s13063-022-07010-4">http://dx.doi.org/10.1186/s13063-022-07010-4</a></p>			<p>(distilled water) for 7 days</p>		<ul style="list-style-type: none"> <li>Alanine transaminase (ALT) (p=0.022), lactate (p&lt;0.001), creatinine (p=0.005), and international normalized ratio (INR) (p=0.049) decreased meaningfully in the intervention arm</li> </ul>
<p><b>Effects of high-dose L-carnitine supplementation on diaphragmatic function in patients with respiratory failure: A randomized clinical trial (2023)</b></p> <p>Abdalla W, DOI: <a href="https://doi.org/10.1080/11101849.2023.2168852">https://doi.org/10.1080/11101849.2023.2168852</a></p>	<p>Prospective, randomized, controlled clinical trial</p>	<p>60 critically ill patients with respiratory failure</p>	<p>Parenteral L-carnitine low dose (6 g/day) versus high dose (18 g/day) as infusions</p>	<p>Serum levels of L-carnitine are positively correlated with the two measures of diaphragmatic function [Diaphragmatic excursion and diaphragmatic thickening fraction (DTf) (p&lt;0.001) High-dose L-carnitine supplementation had rapid and significant positive effects on diaphragmatic excursion</p>	<ul style="list-style-type: none"> <li>Higher serum carnitine levels in the high dosage group</li> </ul>

**Table S27: Carnitine in critically ill population: Ongoing trials**



<b>Patient population</b>	<b>Estimated enrolment</b>	<b>Primary aim</b>	<b>Study design</b>	<b>Trial identifier</b>
Septic shock patients with acute renal insufficiency	272, currently recruiting	To compare 28-day mortality rates between septic shock patients with acute renal insufficiency treated with L-carnitine (as an adjunct therapy) versus placebo	Randomised controlled interventional trial: 6g of L-Carnitine parenteral bolus on Day 1, Day 2 to Day 10: 1 administration every 12 hours of 50 mg/kg/day versus placebo	NCT02664753PHRCN/2015/PR-01